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THE FRANK E. BUNTS INSTITUTE

The Frank E. Bunts Institute will present a course on Blood, Bleeding, and the Blood Vessels on March 16, 17, 18, 1947.

The program of the course is outlined on page 63. Because of building alterations facilities will limit attendance to 125. An application blank is submitted for the convenience of those wishing to avail themselves of this course.

Registration will take place at Cleveland Clinic on March 16, 1947, from 8 to 9 a.m.

(*See Page 63*)

MASSIVE HEMORRHAGE (MELENA) DUE TO LEIOMYOSARCOMA OF THE JEJUNUM

Report of a Case

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Section on Gastrointestinal Disease

This report is submitted because of the rarity of the condition, the fact that the patient presented features of considerable interest from the standpoint of differential diagnosis, and because the lesion is a rare cause for massive hemorrhage from the gastrointestinal tract. A diagnosis of functional indigestion was made at the time of the original examination.

One and a half years later the patient entered the hospital as an emergency case with a blood count of 33 per cent hemoglobin and 2,760,000 red cells. A working diagnosis of peptic ulcer was made because typical hyperacidity symptoms were presented. Three weeks previously detailed roentgen examinations of the entire digestive tract, including studies of the small intestine, had disclosed no abnormality. When the patient did not make a satisfactory response to medical ulcer management, which included five 500 cc. blood transfusions, under our care, Dr. J. C. Root demonstrated abnormality at the site of the lesion by roentgen examination, even though the tumor was extraluminal and caused no obstruction (small diverticulum). He also demonstrated a Meckel's diverticulum, an exceedingly rare roentgenologic finding. The preoperative diagnosis was massive hemorrhage due to "peptic ulcer" in a Meckel's diverticulum.

At operation, performed by Dr. T. E. Jones, no ulceration was found in the Meckel's diverticulum, but an extraluminal mass measuring 6 x 4 x 3 cm. was found in the upper jejunum at the site of the "small diverticulum" previously demonstrated by roentgen examination. Eight centimeters of the jejunum, including the mass, were resected, and an end to end anastomosis was made. The patient had an uneventful convalescence and when seen three months later was well, the blood count normal. However, he had recently had a recurrence of symptoms attributable to "irritable colon", which illustrates the fact that organic disease can be superimposed on functional disturbances. Removal of the former does not correct the latter.

Case Report

First admission; diagnosis "irritable colon". A white man, aged 41, first entered Cleveland Clinic on January 25, 1945, complaining of cramp-like pain across the lower abdomen, chiefly in the left lower abdominal quadrant. Associated with this were marked

gaseous distress, such as bloating and borborygmi, and constipation during the previous eight years. The distress was worse immediately after meals, intensified by ingestion of raw apples, raw vegetables, and cathartics, and was temporarily relieved by the passage of flatus, a bowel movement, or expulsion of an enema. The patient had used large enemas frequently over the eight-year period. He obviously had a stool complex, had observed large amounts of mucus (he believed the amount passed affected his general health for the time being), but had never observed blood or tarry stools. There had been no loss of weight.

Physical examination revealed a man 5 feet 6½ inches in height and weighing 167 pounds. No abnormality except the palpation of an unusually spastic and rope-like sigmoid colon was evident. The introduction of a barium enema reproduced the typical abdominal distress, but roentgen examination of the colon and terminal ileum revealed no organic abnormality. Laboratory examinations, including blood count, blood sugar, blood Wassermann and Kahn tests, and urine examinations also gave negative results.

The diagnosis of irritable spastic colon, due to the self-use of irritating cathartics and large enemas over a period of eight years, was made. A graded residue diet, principles of bowel management, and antispasmodic medications were advised. The patient lived in Cleveland and was instructed to see us if his progress was not satisfactory. In view of these circumstances it did not seem practical to investigate the entire digestive tract in detail at that time.

Second admission: preoperative diagnosis, massive hemorrhage due to "peptic ulcer" in a Meckel's diverticulum. The patient returned to the Clinic on August 9, 1946. It was apparent that his extreme weakness and pallor was the result of serious organic disease, not a functional disturbance. He was not in shock. There had been a weight loss of 19 pounds since his original admission. The blood pressure was 130 systolic and 90 diastolic in mm. of mercury, and the pulse rate was 88 beats per minute and of good quality. Proctoscopic examination revealed normal findings for a distance of 20 cm., as did roentgen examination of the colon and terminal ileum, using a barium enema. However, during the proctoscopic examination chemical tests of the swabs revealed strongly positive tests for occult blood with the benzidine test.

At this stage of the examination a history obtained from several sources revealed the following: The patient had had a massive hemorrhage (melena) on July 1, 1946, and had been treated in a neighborhood hospital. Large clots of both light and dark blood were observed in the stools. Detailed questioning revealed the fact that the patient had been passing blood by rectum during the previous two months and that he presented symptoms characteristic of peptic ulcer. Both blood transfusion and symptomatic care had given temporary relief, but numerous roentgen examinations had revealed no abnormality. When we received the report of the blood count of 33 per cent hemoglobin and 2,760,000 red cells the patient was immediately hospitalized as an emergency case.

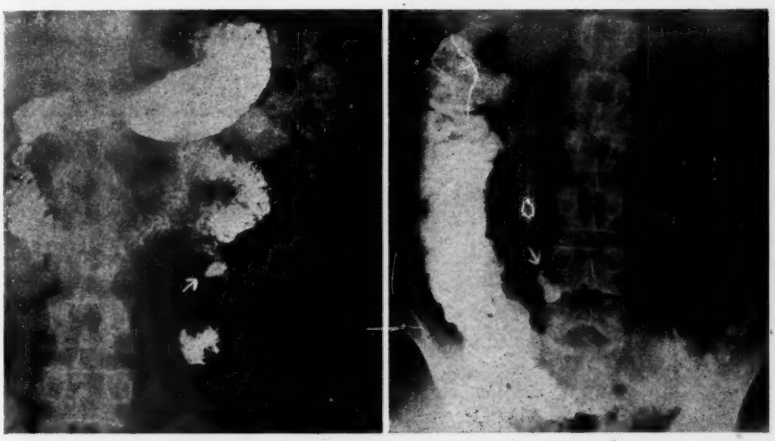
The patient went into shock while attempting to expel an enema and was revived by stimulants and a blood transfusion.

He did not make the usual favorable response to medical peptic ulcer management,[1,2] including five 500 cc. blood transfusions (Meulengracht's method plus the two-hourly use of nonabsorbable antacids) over an eight-day period of time.

Roentgen Examination—Special Technic

By this time several clinicians and roentgenologists had become particularly interested in the problem of this patient. All of the previous x-ray films were obtained and scrutinized closely. Dr. J. C. Root, of the Department of Roentgenology, believed that

too large a barium sulfate meal had been given in previous roentgen examinations of the small intestine. He therefore gave only two swallows of a barium sulfate mixture of 50 per cent barium sulfate and 50 per cent water and made detailed interval studies of the small intestine. Using this technic he demonstrated a "small diverticulum" of the jejunum, about 6 inches from the ligament of Treitz (site of the sarcoma), and a larger diverticulum in the lower ileum (site of the Meckel's diverticulum). Prior to these examinations he had demonstrated no abnormality in the esophagus, stomach, or duodenum (fig. 1).



a *b*

FIG. 1. (a) Roentgenogram showing ulcerating lesion in upper jejunum. (b) Roentgenogram showing Meckel's diverticulum in distal ileum.

Findings at Operation; Resection of Tumor

On August 23, 1946, an exploratory laparotomy was performed by Dr. T. E. Jones A low midline incision was made extending from the umbilicus to the symphysis. The ileocecal valve was located, and every inch of the small intestine was visualized and palpated. Approximately 3 feet from the ileocecal valve a diverticulum of the ileum measuring 5 cm. in length and 1 cm. in diameter was found. The diverticulum was excised over a curved hemostat placed flush with the bowel wall. Closure of the defect was accomplished with a continuous over and over suture line of catgut applied over the clamp, a second continuous suture line inverting in type, and a third suture line of interrupted catgut sutures. The remainder of the small bowel was then examined. Six inches distal to the ligament of Treitz there was a tumor mass arising from the mesenteric border of the jejunum. This was excised by resecting a segment of jejunum 8 cm. in length. The resection was accomplished between Payr clamps, and a small portion of the mesentery was removed along with the tumor mass. An end to end anastomosis of the open type was effected between the two cut ends of jejunum by two continuous suture lines of catgut inverting in type. The small defect in the mesentery opposite the anastomosis was closed with interrupted catgut sutures. The wound was closed with interrupted figure of eight steel sutures, and skin clips were applied.

Pathologic Report
by
John B. Hazard, M.D.

Gross Examination: (Fig. 2) Projecting from the mesenteric aspect of segment of jejunum, 8 cm. in length, is an ovoid mass 6 x 4 x 3 cm., firm, white, with glistening surface and attached to the bowel over an area 3.5 cm. in greatest diameter. On the mucosal aspect there is a deep crateriform ulcer, 1.4 cm. in diameter, 2.3 cm. in depth. Section reveals a friable, rather soft, white tissue with homogenous cut surface. The zone of ulceration extends almost to mesenteric fat tissue in one area. Jejunal mucosa is attached to the mass marginal to the zone of ulceration, but the major portion of the tumor projects outside the bowel.

Also received is an open diverticulum, 2 x 2 cm., with brownish red mucosal surface showing a few folds.

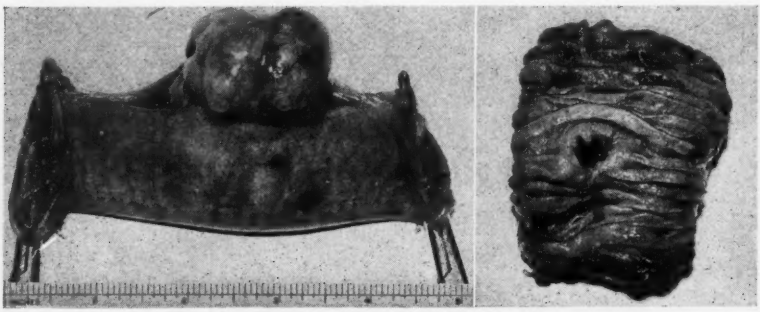


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Fig. 2. (a) Tumor mass projecting from mesenteric aspect of jejunum. (b) Crateriform ulcer of mucosal aspect of neoplasm.

Microscopic Examination: (Fig. 3) The mass is formed principally of spindle shaped cells, arranged in interlacing bundles. In areas the cells are plump and almost polyhedral. Cell cytoplasm is pink-staining and of moderate amount. Nuclei are elongated, oval, or rounded, are moderately vesicular, and occasionally have prominent nucleoli. Occasional tumor giant cells are present. Mitoses are of moderate to frequent number and at times atypical. A rather abundant reticulum is present. Definite myoglia are not evidenced in phosphotungstic acid hematoxylin preparations, but the general configuration is that of a smooth muscle neoplasm.

The diverticulum is lined by a mucosa typical for ileum.

Diagnosis: Leiomyosarcoma, subserous, mesenteric aspect of jejunum, with ulceration and hemorrhage. Meckel's diverticulum.

Comments

In combined surgical and autopsy cases quoted from five sources by Frank, Miller, and Bell[3] there were 38 instances of sarcoma of the small intestine in 117,357 cases, an incidence of 0.03 per cent. Myosarcomas

and fibroscarcomas occur less frequently than lymphocytomas. Bockus[4] states that because of their rarity, the earlier and milder symptoms of small intestinal tumors are often considered to be of functional origin, and valuable time is lost owing to the failure to institute the necessary diagnostic procedures promptly. The initial complaints of most patients with small bowel tumors are those due to obstruction.

Jones and Brubaker[5] reported 22 patients having tumors of the small intestine who had had operations at Cleveland Clinic. Only 1 instance of leiomyosarcoma was encountered in this group. Recently Jones published his experiences in the *Management of Obscure Gastrointestinal Hemorrhage*[6] which included 4 additional case reports of abnormalities in the small intestine, in 2 of which the significant finding at operation was ulceration in a Meckel's diverticulum. In all 4 cases roentgen examination of the

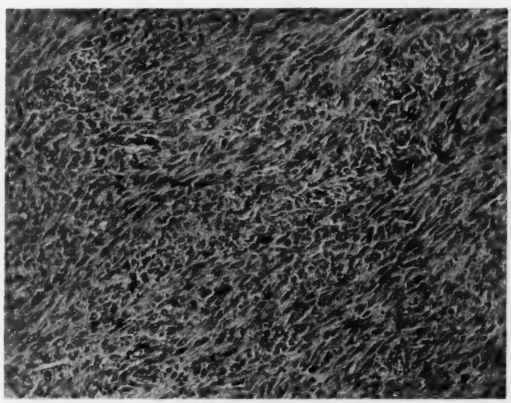

FIG. 3. Interlacing bundles of spindle shaped tumor cells.

gastrointestinal tract had presented normal findings. He emphasized the fact that the small intestine is usually the blind spot in roentgen diagnosis and that although roentgen examination is effective in diagnosis of stomach and colon lesions, it usually has no value in the small intestine except in cases of obstruction.

Several features in the present case report, therefore, deserve emphasis. The patient presented the typical findings for a functional disturbance in the colon when first seen. When last seen three months after the resection of the tumor, he again presented the same findings for the functional disturbance. The first sign of organic disease was massive hemorrhage from the gastrointestinal tract, not obstruction. Even though no obstruction was present and the tumor was extraluminal,

evidence of ulceration was demonstrated at the site of the tumor by roentgen examination. The rare demonstration of a Meckel's diverticulum was also made by roentgen examination. The surgical approach and technic used in this instance has proved significant in our experience with the management of obscure gastrointestinal hemorrhage at the Clinic.

Summary

A rare instance of massive hemorrhage (melena) due to leiomyosarcoma of the jejunum is presented. By the use of special x-ray technic evidence of ulceration at the site of the tumor was demonstrated, even though the tumor was extraluminal and caused no obstruction. A Meckel's diverticulum was also demonstrated in the same patient by roentgen examination.

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ATOMIC ENERGY IN MEDICINE

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Research Division

The atomic bomb has demonstrated to the world in a dramatic fashion that great energies are stored up in atoms and that these energies can be liberated in many forms, such as mechanical, heat, light, ultraviolet radiation, roentgen rays, gamma rays, neutrons, and other subatomic particles. The demonstration of this destructive weapon has kindled in men the desire to use these energies for peaceful pursuits. Among these men the physician ranks first. He believes that the release of controlled atomic energy,[1] notably in the form of radiation, will widen his knowledge of the value of various types of radiant energy in diagnostic and therapeutic procedures.

Although many voices state that a new era, which should be measured in terms of atomic years, began with the year of the destruction of Nagasaki and Hiroshima, the physician knows that the science of atomic physics extends over the last fifty years and that the fundamental principle of atomic fission in particular, upon which the atomic bomb is based, was known before the start of the second World War. The technologic advance in the development of this principle to the point of controlled release of vast amounts of atomic energy is an important accomplishment. It has led to the production of large amounts and a great variety of radioactive materials. But at present only relatively few new radioactive substances or isotopes, such as radio-sodium, radiocarbon, radio-phosphorus, or radio-iodine, are available to the medical profession; they are used for so-called tracer studies as well as treatment purposes. Methods of dosage of such substances are to a large extent still experimental. Procedures for protection against the undesirable effect of such isotopes are known to but relatively few experts, although as a whole these methods are based mainly upon principles worked out in the past by radiologists.[2] A serious word of warning must be sounded against both careless use of any radioactive material and over-enthusiastic hopes regarding the possible cure of numerous diseases by their use. Only experience accumulated in fifty years of atomic physics combined with knowledge gathered from new improvements in the use of atomic energy and its by-products will lead toward a further successful attack on many obscure problems.

For twenty-five years the Research Division of Cleveland Clinic has been actively interested in studies on the use of various types of radiation in medicine. In 1933 this division collected material on the subject and

edited a book, *The Science of Radiology*,[3] which presented a comprehensive picture of the status of atomic energies known at that time. Ten years later the division again collaborated on the publication of two additional books, *Medical Physics*[4] and *Physical Foundations of Radiology*,[2] which brought up to date the picture of the use of atomic energy in medicine and illustrated the rapidly growing importance of this branch of science. A chapter on historic milestones in the fifty years of atomic energy was published in the latter book. That chapter, somewhat enlarged to include developments of the last three years, is presented here in order to familiarize the reader with the historic sequence of events. To many of these notations have been appended additional "Notes, 1946" in an attempt to evaluate past discoveries in the light of the 1946 knowledge of atomic energy.

1895 (November) W. C. Röntgen (Germany) discovered *x-rays* with a Hittorf-Crookes vacuum tube.

1896 (November) J. Perrin (France) measured by means of an air condenser the loss of electric charge caused by ionization produced by x-rays.

1896 A. H. Becquerel (France) presented the results of his discovery of radioactive radiations emitted by uranium compounds. *Radioactivity.*

1897 J. J. Thomson (England) studied deflection of cathode rays by a magnet and came to the conclusion that these rays are streams of discrete particles of negative electricity, considerably smaller than atoms. He applied the name *electrons* to these particles.

1897 E. Rutherford (England) examined Becquerel's radioactive radiations and found them to be composed of two types which he called *alpha* and *beta rays*. Later he found that alpha particles consist of nuclei of helium and beta rays of the electrons discovered by Thomson.

1898 Marie and Pierre Curie (France) announced the discovery of *polonium* in July and *radium* in December.

1898 P. Villard (France) discovered *gamma* rays of radium and found them to be of the same character as x-rays.

1901 M. Planck (Germany) proposed the *quantum theory*, according to which radiant energy is emitted or absorbed in discontinuous steps or quanta.

1905 A. Einstein (Germany) proposed that mass and energy are related by the equation $E=mc^2$, in which E signifies energy, m mass, and c the velocity of light, or 3×10^{10} cm. per second. (Note, 1946:

This famous equation has become of the greatest significance in the calculation of energies available in atomic energy releases. For example: What is the force that holds the helium nucleus together? The basic mass unit of each of the two protons in the nucleus is 1.00758, and of each of the two neutrons, 1.00893. Thus the total mass unit of the nucleus is 4.03302. But the real weight found in the atomic table is only 4.0028, which means that there is a difference of 0.0302. This difference in mass represents the binding energy holding the nucleus together. According to Einstein's formula it amounts to 28 million electron volts.)

1906 H. Geiger (Germany) with Rutherford (England) developed an instrument to detect and count alpha particles. He later improved this counter, at times assisted by Mueller, until it became a most sensitive device for the detection and measurement of many types of radiations. (Note, 1946: The technologic application of the *Geiger counter* in the atomic project program has brought this most valuable tool to the attention of wide scientific and lay circles with the result that it is often considered a new instrument. Actually it had been used successfully in scientific laboratories [2,5] for many years prior to this project.)

1908 P. Villard (France) proposed a dosage unit based upon ionization of air by roentgen rays.

1909 R. A. Millikan (U.S.A.) measured the electric charge of the electron.

1910 F. Soddy (England) suggested the existence of atoms with different atomic mass but identical chemical properties; such atoms would be called *isotopes* (same place).

1911 E. Rutherford (England) proposed an atomic theory according to which the mass and positive charge of the atom was concentrated in its nucleus.

1911 C. G. Barkla (England), in studying scattered roentgen rays, deducted that a number of electrons must exist outside the atomic center.

1912 M. von Laue, W. Friedrich, and P. Knipping (Germany) discovered that roentgen rays can be diffracted by crystals and therewith proved that roentgen rays belong in the group of electromagnetic wave radiations.

1912 C. T. R. Wilson (England) reported on studies of fog tracks produced by various types of corpuscular or wave radiations in his cloud expansion chamber. (Note, 1946: The Wilson cloud chamber has become another invaluable tool in the hands of the atomic

physicists, and fundamental new discoveries have been made with it.)

1913 N. Bohr (Denmark) suggested an *atom model* with a central nucleus and electrons moving in certain orbits around it.

1913 V. L. Moseley (England) studied many roentgen ray spectra of elements and assigned a number to each atom on the basis of these studies. *Atomic number.* (Note, 1946: The atomic number starting with 1 for the lightest element, hydrogen, and rising in sequence to the heaviest "pre-atomic" element 92 for uranium has become of the utmost importance in classifying atoms and in describing their structure.)

1913 Th. Christen (Switzerland) suggested the expression of roentgen ray qualities in half value layers.

1913 W. D. Coolidge (U.S.A.) built the first successful roentgen ray tube with hot filament and tungsten target.

1914 W. H. and W. L. Bragg (England) reported on their roentgen ray spectrometer with crystals as reflecting or refracting diffraction grating.

1914 W. Duane (U.S.A.) presented an "E" unit, based upon ionization, as a measure for roentgen ray intensities.

1914 B. Szilard (France) demonstrated a dosimeter for the measurement of roentgen ray intensity, calibrated in mega-mega-ions.

1916 W. Friedrich (Germany) suggested the *e* unit, or electrostatic unit, as a dosage unit for roentgen rays.

1919 E. Rutherford (England) bombarded nitrogen atoms with alpha particles and found that the nuclei of these atoms disintegrated, giving off hydrogen, while oxygen atoms were left. The particles given off were found to be positively charged, and Rutherford named them *protons*. Historically this was the first experiment in which one element was artificially transformed into another element, namely nitrogen into oxygen. (Note, 1946: Atomic transmutations, of which Rutherford's experiment was the first, can be expressed in equations similar to chemical equations. Rutherford's transmutation reads: ${}_7N^{14} + {}_2He^4 \rightarrow {}_8O^{17} + {}_1H^1$, the letters representing chemical symbols of nitrogen, helium, oxygen, and hydrogen, the subscripts representing the atomic number, and the superscripts the atomic weight.)

1920 F. W. Aston (England) reported exact measurements of masses of many atoms obtained with the mass-spectrograph. He offered evidence that many elements consist of a mixture of isotopes,

therewith furnishing experimental evidence for Soddy's original suggestion in 1910 that such fractions of ordinary elements exist. (Note, 1946: The name isotope has become the most important term in the science of atomic energies. There are *stable isotopes* which, like most elements, do not change with time, and there are unstable or *radioactive isotopes* which undergo changes associated with emission of radioactive radiations. For example, carbon with atomic number 6 has five isotopes, namely carbon-10, carbon-11, carbon-12, carbon-13, and carbon-14. Carbon-12 and 13 are stable, the other three radioactive.)

1920 N. Bohr (Denmark) modified Rutherford's and his own original concept of the atom model, made in 1913, and assigned the electrons to orbits around the nucleus with certain levels of energy. The number of protons in the nucleus determined the number of electrons on orbits outside the nucleus and therewith the place of the atom in the periodic system of elements.

1922 A. H. Compton (U.S.A.) discovered the "Compton effect".

1925 L. DeBroglie (France) suggested that fast-travelling electrons are accompanied by a train of waves. C. J. Davisson and L. H. Germer (U.S.A.) stated that under certain circumstances beams of electrons behave as waves and not as particles.

1925 H. Fricke and Otto Glasser[2,6] (U.S.A.) developed the thimble ionization chamber with "air wall".

1928 Otto Glasser, U. V. Portmann, and V. B. Seitz[2,7] (U.S.A.) constructed the condenser dosimeter for the measurement of roentgen and radium radiations.

1930 W. Bothe and A. Becker (Germany) bombarded beryllium atoms with alpha rays from polonium and obtained carbon-13 and very penetrating rays with no electric charge which they thought to be gamma rays. (Note, 1946: This experiment written in an atomic equation reads: ${}_4Be^9 + {}_2He^4 \rightarrow {}_6C^{13} + \gamma$.)

1930 C. C. Lauritsen (U.S.A.) developed a supervoltage single section roentgen ray tube for atomic investigation.

1931 W. D. Coolidge (U.S.A.) built multisection "cascading" supervoltage roentgen ray tubes.

1931 E. O. Lawrence (U.S.A.) invented the *cyclotron.*[8] In 1933, collaborating with M. S. Livingstone (U.S.A.), he built a cyclotron capable of producing five-million-volt deuterons. In further constructions sixteen-million-volt and then 100-million-volt deuterons were attained. (Note, 1946: A 200-million-volt deuteron cyclotron is scheduled to be in operation shortly.)

1932 H. C. Urey (U.S.A.) discovered heavy hydrogen, which he called *deuterium*. Its nucleus, *deuteron*, has mass 2 and consists, as was established later, of 1 proton and 1 neutron. This nucleus plays an important role as a bullet in atomic-smashing experiments.

1932 J. Chadwick (England) announced discovery of the *neutron*, a neutral nuclear particle of about the same mass as the positively charged proton. This experimental proof of the existence of the neutron confirmed speculations made by Rutherford in 1919. (Note, 1946: The formula for Chadwick's discovery is essentially the same as Bothe and Becker's formula, described previously under the year 1930: ${}_4Be^9 + {}_2He^4 \rightarrow {}_6C^{12} + {}_0n^1$, but it contains Chadwick's discovery of a new particle, the neutron, which in certain respects behaves like gamma rays. Bothe and Becker did not realize that they dealt with a new type of radiation in their experiment and they narrowly missed making the great discovery of the neutron.)

1932 W. Heisenberg (Germany) explained theoretically that the atomic nucleus consists of protons and neutrons.

1932 J. D. Cockroft and E. T. S. Walton (England) disintegrated lithium with 700 kv. protons and found that mass is converted into energy during the disintegration.

1932 D. H. Sloan and E. O. Lawrence[2] (U.S.A.) constructed a radio-frequency supervoltage roentgen ray generator. (Note, 1946: L. W. Alvarez is building a "linear accelerator" on this same principle, which promises to produce radiations of more than 300 million electron volts.)

1932 L. S. Taylor (U.S.A.) developed an American standard air ionization chamber to determine the value of the *roentgen*.

1933 R. J. Van de Graaff (U.S.A.) built electrostatic generators capable of producing voltages up to 10 million volts.

1933 C. D. Anderson (U.S.A.) discovered the *positron*, the electric counterpart of the electron.

1934 F. Joliot and Irene Joliot-Curie (France) produced *artificial radioactivity* by bombarding aluminum with alpha particles and observing that neutrons and positively charged particles were emitted from the aluminum during this process. (Note, 1946: The formula for this experiment is: ${}_{13}Al^{27} + {}_2He^4 \rightarrow {}_{15}P^{30} + {}_0n^1$. The produced isotope of phosphorus, being unstable, disintegrates into silicon accompanied by emission of positrons according to the formula: ${}_{15}P^{30} \rightarrow {}_{14}Si^{30} + {}_{+1}e^0$.)

1935 E. Fermi (Italy) bombarded uranium and other atoms with deuterons and neutrons and observed many phenomena of artificial transmutation and radioactivity. Shooting slow neutrons into uranium he produced new "trans-uranium" elements, notably one with the atomic number 93.

1936 J. H. Lawrence, R. E. Zirkle, and P. Aebersold (U.S.A.) found that neutrons have profound biologic effects.

1937 The Fifth International Congress of Radiology accepted the *roentgen* as an international dosage unit.

1939 The treatment of cancer patients with the neutron beam from a cyclotron was started by E. O. Lawrence and R. S. Stone (U.S.A.).

1939 O. Hahn and F. Strassman (Germany) bombarded uranium-235 with neutrons and demonstrated that it broke into two large fragments with atomic masses of about 142 and 91. L. Meitner and O. Frisch (Germany) reasoned theoretically that in this "*fission*" of uranium great amounts of energy are released. O. Frisch, F. Joliot, N. Bohr, J. R. Dunning, H. O. Nier, and others confirmed experimentally the prediction that uranium-235 can undergo fission.

1940 Two new elements were created from uranium by neutron bombardment; they are neptunium, atomic number 93, and plutonium, atomic number 94. (Note, 1946: The formulae for the production of these new elements are:

$$_{92}U^{238} + {}_{0}n^{1} \rightarrow {}_{92}U^{239} + \gamma \rightarrow {}_{93}Np^{239} + {}_{-1}e^{0}$$

$$_{93}Np^{239} \rightarrow {}_{94}Pu^{239} + {}_{-1}e^{0} + \gamma.$$

1940 Several hundred artificially created *radioactive isotopes*[9] had been discovered. Some were used for treatment, others served as tracer substances to trace physiologic processes.

1940 D. W. Kerst (U.S.A.) constructed the *betatron*,[10] with which electrons are accelerated to energies of 20 million electron volts by magnetic induction. (Note, 1946: A number of betatrons were constructed, the largest at present delivering electrons with energies up to 100 million electron volts. An improved betatron, called *synchrotron*, proposed by McMillan and promising energies up to 300 million electron volts, is under construction now.)

1942 (December 2) First self-maintaining nuclear chain reaction in an *uranium graphite pile* was initiated.

1945 Atomic bombs were exploded on July 16 in New Mexico, August 6 in Hiroshima, and August 11 in Nagasaki. Official report on *Atomic Energy for Military Purposes* was published.[1]

1945 G. T. Seaborg (U.S.A.) announced discovery of elements americium, atomic number 95, and curium, atomic number 96.

1946 Headquarters, Manhattan Project, Washington,[11] announced the availability of a number of tracer and therapeutic radioisotopes to scientific laboratories. First shipment of fission products for scientific research was made from Oak Ridge, Tennessee.

1946 G. T. Seaborg (U.S.A.) announced the discovery of neptunium-237, a slow isotope of neptunium-239, discovered in 1940. Neptunium-237 is the fourth element in which atomic energy is released by nuclear fission; the other three are uranium-235, plutonium-239, and uranium-233.

To the medical profession, the great scientific events condensed in the preceding chronology of developments in atomic energy offer many new opportunities in the endeavor to fight disease. Developments of the last few years have considerably enhanced the scope of these possibilities.

Atomic energy as used in medicine may be divided into two parts, *electronics* and *nucleonics*. Electronics comprises that part which has to do with the electrons revolving around the nucleus of atoms. Most phenomena observed by the physician, such as chemical reactions, optical, electric, magnetic effects, have to do with these electrons. In the roentgen ray tube, electrons emitted from the cathode are accelerated by the applied high voltage and, when suddenly stopped at the target, are transformed into roentgen rays. When roentgen rays hit the fluoroscopic screen, the photographic film, or tissue, they first knock out electrons from the matter hit. These electrons are subsequently responsible for the reactions observed, such as fluorescence, darkening of the film, erythema, or other biologic reaction of tissues. Multimillion-volt Van de Graaff electrostatic generators, betatrons, or synchrotrons capable of producing high energy roentgen rays and electrons will enlarge the field of application of roentgen rays and lead to new observations in medical radiology. Other electronic devices in medicine consist of the application of improved amplifier circuits to such well known devices as the electrocardiograph, the electrostethoscope, and the electro-encephalograph. Improved photo-electric devices such as the multiplier photo-cell have greatly improved roentgen ray exposure meters, plethysmographs, and other devices. An ingenious use of steering devices for electrons has led to the development of electromagnetic lenses and condensers, which in their practical development have resulted in the construction of electron microscopes which have multiplied many times the amplification powers of standard microscopes. A whole new branch of science has been built upon this foundation, the science of electron optics.

The widespread application of electronics in medical instruments is being overshadowed at present by nucleonics. The reason for this lies in

the fact that the amount of energy stored up in the atomic nuclei is millions of times greater and has, therefore, if released, effects which supercede by far those produced by electronic energies. To a limited extent the radiologist has been familiar with the release of atomic energies, since he has used radioactive substances for decades and has known that they decay continuously and in doing so emit alpha, beta, and gamma rays. In decaying, a transmutation takes place. The fact that metallic radium element, for instance, decays into two gases, namely radon and a helium nucleus, has demonstrated that by atomic changes one element can be transformed into another of entirely different physical properties. Beta and gamma rays have long been used for therapeutic purposes. Radium dosages had to be measured properly and precaution taken for protection against undesired radiation effects upon patient and operator. In principle, established dosage units and terms such as the curie, the roentgen, and tolerance dose have been maintained in recent radioactive isotope work. Similarly, protection methods against undesirable radiations are like those used in prefission days, although the technologic improvements in ionization chambers and Geiger counters have been great.

However, the process of fission developed in atomic research of the last few years, in addition to radioactive decay and transmutation, has furnished the medical profession not only with new methods of producing radioactive substances but with a large variety of such substances of great intensities. Powerful uranium and plutonium piles in themselves produce numerous radioactive fission products, i.e. radioactive isotopes with atomic numbers near the middle of the periodic atomic table. Neutrons released in these piles, furthermore, can activate any materials placed into the pile. This artificial radioactivity may be used in various ways. One might, for instance, use penetrating radiations emitted from the pile for therapeutic purposes. Such a radiation beam might possibly be a neutron beam similar to that emitted from the cyclotron, and such a beam might activate chemicals introduced into certain parts of the body. Other elements made radioactive in the pile may subsequently be used as radiation sources for treatment similar to the technic employed in the radium pack. And finally, given atoms might be made radioactive and introduced into the body with the plan to have them absorbed selectively in organs or in tumors or any place where specific radiation doses could be applied at the desired site of the tissue. In the same way atoms could be made radioactive or they could be "tagged" to act as tracers in the human body. As long as they are active they could be traced throughout body fluids or tissues in a way rather similar to the tracing of a lost radium container by means of sensitive devices such as a Geiger counter. Long before the era of tracing radioactive isotopes through the body with Geiger counters, physicists have tracked

down lost radium through furnaces, ash cans, trucks, city dumps, and final resting places of cinders miles away from the furnace through which the radium tube passed.[12] Modern tracing hunts are very similar. They permit the investigator to follow certain given isotopes in a compound or a mixture through liquids, gases, or solids. Blood flow and blood volumes can thus easily be measured. Circulation and its impairments in peripheral vascular diseases can be studied with radioactive sodium and the extent of such diseases revealed. Similarly, the path of drugs, poisons, and anesthetics can be followed throughout the body to their elimination or final resting place. Radioactive dyes can easily be localized. Tracing radioactive iron or phosphorus in blood cells has revealed important information on their formation and life. Radioactive carbon has helped studies on basal metabolism, breaking down of food, of diabetes, tooth decay, and other bodily changes. Radioactive gases such as krypton have opened new roads to studies on respiration, vascular diseases, and arteriosclerosis.

Accumulation of such radioactive isotopes in certain locations has helped in the treatment of leukemias and polycythemias with radioactive phosphorus, of thyroid diseases with radioactive iodine, of arthritis with radioactive gold, and of cancers with radioactive strontium.

In conclusion, it may be stated that scientific research in releasing and controlling atomic energy and related problems has vastly enlarged the field of medical radiology and has presented medicine with a great number of new materials and new tools for use in medical research as well as for practical application in clinical problems.

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OSTEOMA OF THE FRONTAL SINUS

Report of Two Cases

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Although osteoma of the frontal sinus is not rare, the following 2 cases present some features of special interest. Osteomata are usually found on routine examination in the early stage, as in the first examination of case 1, or not until they have produced symptoms, as in case 2. The opportunity seldom arises to observe their development from innocent, rather unimportant findings to the obstructing, dangerous stage as in case 1. Osteomata are slow growing and usually do not reach a size that requires operative interference. Although they are more prone to increase in size during youth, the growth in case 1 occurred during the period between the ages of 38 and 46.

Case Reports

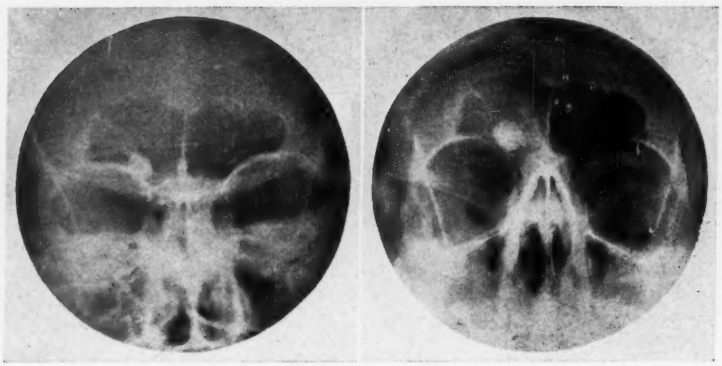
Case 1. A man, aged 36, was first seen on September 24, 1937, complaining of nasal congestion and chronic purulent postnasal drip. He had had a submucous resection seventeen years previously with some relief of nasal obstruction but with subsequent nasal crusting. Family history revealed that both grandfathers had suffered from asthma, one having had hay fever as well. The patient had had eczema in infancy and had noted sneezing and nasal congestion on exposure to horse hair and dust.

Examination showed a straight nasal septum with a large anterior perforation. Turbinates were edematous and pale. There was a large polyp in each middle meatus. The frontal sinuses were clear, the left antrum was dim and the right antrum dark on transillumination. The tonsils had been removed. The larynx was slightly injected but otherwise normal. Both tympanic membranes were normal. Roentgenograms of the sinuses showed a small osteoma in the right frontal sinus (fig. 1a) but were negative otherwise.

The patient was referred to the Department of Allergy for further study and treatment. Removal of the polyps was recommended, and he was informed of the presence of the osteoma and that it might increase in size.

In spite of allergy management the nasal polyps increased in size and number, so that bilateral ethmoidectomy was performed on April 28, 1938. The sphenoids were not involved and therefore were not disturbed. The postoperative course was uneventful, and the nasal allergy was kept under control. There was no recurrence of the nasal polyps.

The patient was next seen on June 1, 1946, complaining of right frontal headache of ten days' duration. The headache was of a throbbing nature and would start about 8 a.m., gradually increasing in intensity and lasting for two or three hours. He recalled being told of the presence of a small osteoma in the right frontal sinus in 1937 and consulted his otolaryngologist with this in mind. Roentgenograms showed a greatly enlarged osteoma in the right frontal sinus filling the region of the opening of the nasofrontal duct (fig. 1b).



a *b*

FIG. 1. Case 1. (a) September, 1937 (b) June, 1946.

On June 12, 1946, an external frontal operation was performed on the right side, and the entire floor of the right frontal sinus was removed. Just enough of the anterior wall was removed to permit delivery of the osteoma, which was 3.5 x 2 cm. and rather firmly attached at its base. Thick mucopus was trapped above and laterally to this mass. Cultures of this material were sterile. The sinus was cleaned of foreign material. The lining mucosa appeared normal, and neither it nor the nasofrontal duct were disturbed. A small rubber tissue drain was placed in the wound at the inner end of the eyebrow, and the wound was closed with interrupted dermal sutures. The drain was removed after twenty-four hours. The patient experienced diplopia for about two months, but there was no recurrence of the headache and no difficulty from collection of fluid in the frontal sinus.

Case 2. A man, aged 25, was first seen February 22, 1943, complaining of a swelling of his right eye of two weeks' duration. This had been preceded by an acute upper respiratory infection with nasal congestion and discharge and sore throat. There had been little or no fever. Severe headache was present in the right frontal area, tending to increase in severity in the evening and at night. The patient had experienced an attack of acute right frontal sinusitis six years previously. The symptoms of this condition had responded to conservative treatment, and the patient had had no further trouble other than a chronic mucoid postnasal drip until the present illness.

The temperature was 99.8°. There was marked swelling and redness of the right upper eyelid, tender to palpation and presenting an area of fluctuation. The eye itself was not involved. The nasal septum was not obstructive. The turbinates on the right side were swollen, and mucopus could be seen on this same side in the nasopharynx and posterior naris. The tonsils were large but not acutely inflamed, and the larynx and ears were normal. Roentgenograms of the skull showed a large osteoma in the right frontal sinus, apparently arising from the ethmoid bone (fig. 2). The right frontal sinus was clouded. Wassermann and Kahn tests were negative. Red blood cell count was 5,030,000, hemoglobin 78 per cent, white blood cell count 5600, and blood sugar 89 mg. per cent three hours after a meal.

An incision made in the right upper eyelid over the point of fluctuation released a large amount of pus which on culture proved to be due to Staphylococcus albus. A

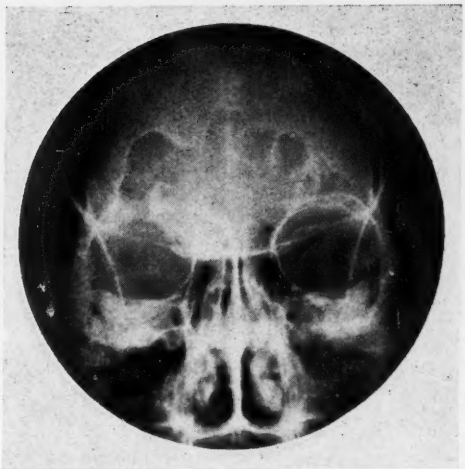


FIG. 2. Case 2. Loss of floor of right frontal sinus and of partition between the frontal sinuses.

neurologic examination revealed no evidence of intracranial extension. The active inflammation subsided during the following week under conservative treatment. It was felt that he was now ready for surgical removal of the osteoma.

The patient was admitted to the hospital on March 3, 1943, and an external frontal operation was performed the next day. The outer plate and floor of the frontal sinus was found markedly thinned, with several areas of dehiscence. The entire floor and a large area of the anterior wall was removed in order to deliver the osteoma. The sinus contained some thick purulent exudate. The osteoma weighed 17 Gm. and measured 4 x 2 x 3.5 cm. It was lightly attached to the ethmoid area and broke away quite easily. The septum between the right and left frontal sinuses had been destroyed by the growth of the osteoma. The nasofrontal ducts were not disturbed. A rubber tissue drain was inserted at the inner end of the brow, and the wound was closed with interrupted silkworm-gut sutures. The drain was removed on the second postoperative day and the sutures on the fourth. The patient was discharged on the sixth postoperative day.

Summary

Two cases of osteoma of the frontal sinus requiring radical surgery are presented. In case 1 the period between the discovery of the tumor and the time when it attained a sufficient size to cause trouble was nine years. The patient was apprised of its presence at the first examination. When the symptoms developed he investigated its status before extensive infection and damage had taken place. The second case illustrates how grave the situation may become when the growth is advanced and is accompanied by inflammatory processes.

EDEMA III. TREATMENT

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The treatment of edema is at first directed toward correction of the causal mechanisms. These were reviewed in the first paper of this series, the clinical states in which they act discussed in the second. Since in many diseases more than one mechanism operates in causing edema, the treatment of different types overlaps. Some of the abnormal mechanisms are not wholly reversible. In such cases treatment is aimed toward symptomatic relief rather than radical cure.

GENERALIZING EDEMAS

Cardiac Edema

Cardiac edema, the most important, is also the most common and easily treated form; it is that which occurs in chronic congestive cardiac failure. The principles underlying its treatment are: (1) rest, (2) digitalization, (3) restriction of sodium salts, (4) diuresis by drugs, and (5) diuresis by water. These principles apply to forms other than cardiac edema. Their application is, therefore, discussed in detail under the present heading only.

Rest

By complete bed rest is usually meant that the patient at all times must lie quietly in bed. While bed rest is essential, in cardiac failure the rule is relaxed to greater or less degree. Adherence to complete bed rest may be quite as dangerous as the effort it seeks to avoid.

Thus the patient with congestive cardiac failure is nearly always more comfortable in the sitting or semi-sitting position than in the supine posture and will naturally assume this position. Imposition of a recumbent posture in the presence of massive cardiac edema may increase discomfort by translocating fluid from the limbs, where it may be harmless, to the body cavities, where it is dangerous. The ideal bed for the patient with cardiac failure is the so-called "cardiac" bed. This can

be adjusted from the recumbent position to one in which the patient sits upright. When this is not available, the customary hospital bed with Gatch frame can be adjusted so that the back and knees may be raised. If the patient is not comfortable in such a bed, an arm chair large enough to permit the use of bedclothes is a practical alternative. In the home an ordinary bed may be improvised to accommodate the orthopneic position by placing pillows at the back, sometimes supported by a kitchen chair and pillows under the knees. It is important to secure these improvised supports so that they do not slip and leave the patient in a position of strain.

Whatever the choice of bed and posture, it is desirable that the patient change his position, with assistance if necessary, several times a day. In general the patient is allowed to sit in a chair for one or two hours daily. Bathroom privileges are usually better permitted than forbidden, at least when such visits do not require much walking. When they do, a simple substitute is the commode, the convenience of which contrasts with mental and physical stresses imposed by the bedpan.

These relaxations of the rule of rest do not apply to the patient whose condition is the result of acute myocardial disease such as that which follows myocardial infarction, although even in this state some relaxations from total rest are desirable, e.g., passive movements of the legs and arms.

Digitalization

Digitalization of patients with chronic congestive failure is best accomplished orally. It is doubtful whether the risks of intravenous therapy, however slight, are worth-while in this condition.

The preparations used are tablets of digitalis leaf and tablets of purified digitalis glucoside. The tincture has fallen into disuse because its potency is always uncertain and the dosage subject to vast errors of measurement.

Digitalization depends on attaining within a reasonable time an adequate concentration of digitalis glucoside in cardiac muscle. Until this concentration has been attained, the full therapeutic action of the drug is not exerted. The exact dosage which will have this effect on any patient is not easily predicted. In the past it has been estimated from body weight. For an adult of average body size the present general rule is that 18 to 21 gr. of digitalis leaf should be given in divided doses during forty-eight to seventy-two hours. It may be given more rapidly if the situation demands, although in such a case the purified glucoside is probably preferable. The dosage of digitalis leaf necessary to maintain

the desired concentration of glucoside in the myocardium is about 1½ gr. per day. Larger doses are often temporarily desirable at the beginning of treatment. The final dosage level is determined by persistence of a full clinical effect without toxic manifestations. The clinical effect is gauged from symptomatic relief and a resting ventricular rate of between 60 and 80 beats per minute.

Among the various purified glucosides with digitalis action, the most generally useful is the glucoside of Digitalis purpurea, digitoxin, therapeutically just as effective as the leaf. It is sometimes preferred because it is less nauseating. It is also more useful when digitalization must be rapidly obtained. The digitalizing dose in adults is 1.2 to 1.5 mg. This amount may be given orally in divided doses over a period of twenty-four hours or, if desired, the whole may be given at one time. Oral administration of the full dose yields a therapeutic effect in about six hours, so that intravenous digitalization is rarely necessary. When an instant effect is desired, the full digitalizing dose may be given intravenously. The maintenance dose of digitoxin is 0.1 to 0.3 mg. daily and, as with the leaf, varies somewhat with the individual.

Regardless of the preparation used, it is essential that no glucoside having digitalis action be given in full dosage for a week or ten days after the last use of digitalis or other cardiac glucoside with prolonged activity.

The rapid shrinkage of plasma and interstitial fluid volume which may result from diuresis in a patient with congestive failure sometimes proceeds more rapidly than the excretion of the digitalis glucoside. The result is accumulation of the glucoside to toxic levels with the consequent manifestations of toxic action, e.g., coupling of the pulse, nausea, and diarrhea. Should this supervene, the dosage of digitalis is temporarily interrupted.

Sodium Restriction

Sodium restriction has as its aim the reduction of sodium intake below the level of average sodium loss. The principal mode of sodium intake is in the form of sodium chloride. The least stringent form of sodium restriction, therefore, consists in forbidding the addition of extra salt to that ordinarily used in cooking and in omitting salt meat, fish, or breads from the diet. This has the effect of reducing salt intake from 5 or 10 to about 3 Gm. daily. Further restriction is accomplished by forbidding the use of salt in cooking meats and vegetables. The intake is thereby reduced to between 1 and 2 Gm. Salt intake may be further reduced to less than 1 Gm. by the use of salt-free bread and butter.

A salt-poor diet is often distasteful and the cause of much complaint. However, the patient should be made to realize that such a diet is an essential part of the treatment of edema and that adherence to it will be well worth-while. Salt substitutes so far in use have been unsatisfactory. Some of them actually contain sodium and thus defeat their purpose. Others are distasteful. A few patients find that the use of a shaker containing potassium chloride adds some flavor to their food, while others find it nauseating. For those who use it, it has the advantage of stimulating water loss.

Diuretics

The most important diuretics in the treatment of congestive heart failure are the mercurials. These act on the kidney by inhibiting reabsorption of sodium chloride, thus initiating water loss from interstitial fluid. Their action is one of controlled and highly selective intoxication of tubular cells. The fears once felt that such an action might in the long run impair renal function have not been realized. Many patients have been kept in fair comfort by the frequent use of mercurials over periods of months and years.

The toxicity of mercurial diuretics is more often cardiac than renal. In spite of the millions of doses given, there is no more than a scattering of reports of severe reactions. These reactions are usually immediate and take the form of ventricular fibrillation. When distress is or has been experienced during injection of the drug, the injection should be stopped. Any later similar medication should be given intramuscularly or rectally rather than intravenously. It has been suggested[1] that magnesium sulfate administered intravenously will prevent the toxic myocardial action of the mercurials if given just before the injection of the diuretic.

The most satisfactory and least irritating mercurials in present use are those which combine an organic mercurial compound with one of the xanthines. These are usually made up so that the therapeutic dose is about 2 cc. The smallest effective dose (0.25 to 2 cc.) is given intramuscularly or intravenously. When given intravenously it is preceded by a test dose of 0.25 cc. The injection is always made slowly, taking about three minutes. It is repeated every three to five days according to need. The drugs may be safely given over long periods if necessary.

Ammonium chloride and ammonium nitrate in doses of 30 to 90 gr. (2 to 6 Gm.) daily are given either alone or in conjunction with mercurials. These salts acidify the urine, thus causing sodium and water loss. They thereby add to and potentiate the effect of the mercurial. They are most palatably given as enterically coated tablets. However,

the contents of the tablets are sometimes not absorbed, and the expected effect is not obtained. In such cases the salts may be given as elixirs. The use of the acidifying diuretic salts may be continued over long periods.

The xanthine compounds, although possessed of some diuretic action, have little significant effect in the treatment of edema as such. They are used in the treatment of congestive failure for their other activities.

Water

The dictum that water is the best diuretic has been revised in recent years and supplemented by convincing clinical study.[2] This represents a reversal from the view that edema should be treated by water restriction. It is a correlation of clinical treatment with physiologic principles.

At the least, provision of water *ad lib.* increases the patient's comfort and, as long as sodium is restricted in the diet, cannot increase edema. Schemm[2] goes far beyond this and utilizes the chloride loss caused by water diuresis. His regime for the treatment of edema, which applies principally to cardiac edema, has as its basis the administration of from 6 to 8 liters of water daily. The exact amount given and the manner of its administration depends on the condition of the patient. It is difficult to give all of it orally, although as much as possible (2 to 5 liters) may be given hourly as glasses of water acidulated by addition of a few drops of dilute hydrochloric acid. The deficit is made up in an intravenous injection of 5 per cent glucose in water.

This regime is accompanied by severe sodium restriction, the degree of which is gradually relaxed as edema lessens. It is supplemented by routine use of one of the acidifying diuretic salts.

It should be noted that water diuresis permits the kidney to excrete substances which might otherwise be retained, so that such treatment not only washes out salt and water but also tends to relieve nitrogen retention due primarily to cardiac failure.

Nephritic Edema

To the extent that the edema of acute hemorrhagic nephritis is inflammatory and due to local vascular or renal glomerular injury, it is not amenable to specific treatment.

The edema of acute nephritis of insidious onset may be considered the same as that of the nephrotic stage of chronic glomerulonephritis into which it insensibly merges.

The principles of treatment of nephritic edema are: (1) sodium restriction, (2) administration of adequate dietary protein, and (3) diuresis by acidifying salts and plasma proteins.

The method of sodium restriction in nephritic edema is the same as that described for cardiac edema.

Protein is given to the patient with nephritic edema in an amount sufficient to establish a normal intake (1 to 1.5 Gm. per kg. daily). This amount of protein is supplemented by an amount which compensates for that lost in the urine and by a further supplement which makes up for any protein deficiency established previously by protein deprivation. The total dosage given adults should not exceed 2 Gm. per kg., and it is usually desirable to give rather less than this. While a high protein diet may compensate for urinary loss and previous protein starvation, it cannot be expected to correct that part of the hypoproteinemia which reflects the underlying renal lesion.

Some of the protein intake may be made up with amino acids given orally or intravenously, although in most patients suitable dietary protein is both cheaper and more palatable. The amino acids have their principal but rare application in the treatment of the hypoaminoacidemic crises of nephrosis. Here they specifically restore the temporary deficit of blood amino acid. It should be recognized that the amino acids have no specific effect on the course of protein metabolism.

Among the drug diuretics only the acidifying salts have proved useful in nephritic edema. Their application lies largely in their promotion of sodium loss, thus supplementing the dietary regulation of sodium intake.

Intravenous injection of a sufficient amount of osmotically active colloid causes temporary diuresis in patients with nephritic edema. Thus acacia has been widely used but more recently discarded in favor of plasma and serum albumin. Intravenous injection of plasma or of the much more expensive serum albumin results in temporary diuresis and is therefore useful when edema has advanced to a dangerous or crippling degree. It does not correct the underlying disability, which is hypoproteinemia.

When proteinuria is severe and the number of urinary casts great, it is probably desirable to substitute potassium citrate for the acidifying diuretic salts. This chemical, in doses of 60 to 90 gr. daily, tends to maintain the urine at a neutral or slightly alkaline reaction, thus inhibiting the precipitation of casts within the renal tubule, while it also tends to wash out salt and water.

A few cases of seemingly intractable nephritic edema have been relieved by renal denervation. The mechanism of the effect is unknown, and this means of treatment is still experimental.

Hepatic Edema

Edema in hepatic disease is either generalizing and due to hypoproteinemia or localized, as ascites, the result of portal hypertension. In either case the provision of a high protein, high caloric diet such as that recommended by Hoagland[3] may be dramatically effective in arresting or even reversing the course of the disease.

The patient is encouraged to take at least 3600 calories daily consisting of 150 Gm. each of animal protein and fat supplemented by carbohydrate. The fat is given chiefly as milk, cream, and butter, but not as fat that has been brought to a high temperature, such as bacon. It is believed that the aldehydes and ketones formed in fat at high temperatures are injurious. The patient is given as much carbohydrate as he will take. In general, patients should double their caloric intake within a week.

Crude liver extract is given in large doses. Extracts intended for this use are now commercially prepared. The appetite often improves markedly after liver administration.

Fifty to 100 Gm. of human albumin is given intravenously. This often causes an immediate positive nitrogen balance which lasts for several weeks. This may be augmented by administering 500 to 750 cc. of plasma per week for four weeks.

Nutritional Edema

Nutritional edema responds to a diet which corrects the varied deficiencies of protein, iron, and vitamins.

Endocrine Edema

Premenstrual edema and tension states may respond to the use of acidifying diuretic salts during the ten days before the menstrual period. When this treatment is not wholly effective, injection of progesterone (5 to 10 mg. daily for three days before the period) or oral use of anhydro-hydroxyprogesterone may prevent the disturbance.

Localizing Edemas

Most of the localizing edemas result from local causes which require surgical correction. Their treatment does not enter into this discussion.

The most frequent among them are the edemas of venous origin. Thrombophlebitis is best treated during its onset by anticoagulants such as heparin or dicoumarol, which prevent its spread. At the onset, and

even in the later stages, lumbar sympathetic block may result in dramatic relief of pain and edema.

Phlebothrombosis is most commonly a complication of bed rest incidental to surgical operation. It is prevented by routine active and passive movements and massage of the limbs and early mobilization of the patient. Once it has developed, anticoagulants should be used. Ligation of the deep veins, especially of the femoral vein, is still a controversial procedure, although certainly justifiable in patients who have shown evidence of pulmonary embolization.

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RADICAL RESECTION OF CARCINOMA OF THE HEAD OF THE PANCREAS

With Report of a Case in a Man of 78

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It is only in the past ten years that patients with carcinoma of the head of the pancreas have been offered a possibility of cure by surgical excision of the head of the pancreas and duodenum. The high mortality rate that at first attended this extensive procedure has been lowered by the discovery of vitamin K and by technical improvements in anastomosing the pancreatic and biliary ducts to the intestine. Mortality rates for large series of radical resections of the pancreas as low as 20 per cent have been reported,[1] a figure which corresponds favorably with that attending radical resections of gastric or intestinal carcinomas fifteen years ago.

Although the curability rate of carcinoma of the pancreas is still low the palliation afforded by radical resection with implantation of the common bile duct and the pancreatic ducts into the intestinal tract renders the operation well worth-while to those patients whose tumor has not extended beyond the pancreas. Not only do these patients have the nutritional advantage of the draining of both bile and the external secretion of the pancreas into the intestinal tract, but they have the knowledge that the tumor has been removed and that they have a chance for permanent cure. This attitude is to be compared with the hopelessness of the patient who is subjected to an exploratory operation and learns that he has an incurable cancer and can do nothing but await the inevitable end.

Cancer of the head of the pancreas is in general no more malignant, no more invasive, or no more prone to rapid growth or early metastasis than other carcinomas of the gastrointestinal tract. It would probably compare favorably in these respects with carcinoma of the stomach and somewhat unfavorably with carcinoma of the colon. The chief reason for the relative incurability of carcinoma of the pancreas is the failure to establish an early diagnosis.

Carcinoma of the head of the pancreas evades early diagnosis because the only physiologic disturbance incident to the early stages of the disease is obstruction of the pancreatic duct. Unfortunately this obstruction rarely causes symptoms more severe than a vague sense of

abdominal discomfort and loss of weight. These symptoms are so diffuse and poorly localized that the patient may not consult a physician, and when he does the evidence of carcinoma of the pancreas is seldom conclusive enough to justify an exploratory operation. If every patient complaining of slight loss of weight and appetite and vague abdominal distress were subjected to an exploratory laparotomy there would be too many useless operations, and if all patients so explored who were found to have suspicious areas of indurations in the pancreas were subjected to radical pancreatoduodenectomy, a significant number of patients with inflammatory lesions of the pancreas would doubtless be subjected to radical operations. Enough of these would probably die after operation to outnumber the patients with carcinoma who would obtain a permanent cure. Biopsy is not of great value in differentiating benign from malignant lesions because the carcinoma is often deep seated, and the specimen removed from the surface shows only fibrosis. We are therefore forced to concede that the accuracy of diagnosis of early carcinoma of the pancreas, either in the clinic or on the operating table, is unsatisfactory and that there is, at the present time, no accurate means of establishing the diagnosis until the chances of permanent cure of carcinoma of the pancreas are lower than the chances of permanent cure in most other types of carcinoma. Radical surgery must consequently be undertaken only when there are excellent indications that (1) the lesion is truly a carcinoma and that (2) the carcinoma is at least potentially curable.

It is not until a carcinoma of the head of the pancreas extends out of the pancreas itself to involve the common bile duct that the definite and localizing symptom of jaundice occurs. But as in the case of carcinoma elsewhere, when the tumor has extended out of the organ in which it originates to involve another organ, the prognosis is of necessity poor. What is needed is a means of detecting the presence of a carcinoma of the pancreas while it is still confined to the pancreas and is still potentially curable.

Carcinoma of the body and tail of the pancreas does not block the main pancreatic duct, as does carcinoma of the head, and hence is apt to cause no symptoms until metastasis occurs or until direct extension of the tumor involves the nerve roots. Carcinoma of the head of the pancreas often originates in or near the main duct and is liable to cause obstruction relatively early. Unfortunately, however, the only method of ascertaining whether or not the pancreatic duct is occluded is by study of the ferments in the duodenum. Since the pancreatic ferments differ but slightly from those secreted by the intestine our deductions must be based on quantitative changes which may be dependent on a

number of factors, including the position of the drainage tube. Analysis of the fat content of the stools gives little help because some patients who have had complete pancreatectomy show little disturbance in the assimilation of fat.

Since there is no specific laboratory test by which carcinoma of the head of the pancreas can be recognized with accuracy before the onset of jaundice, we are forced to wait in most cases until jaundice occurs before making the diagnosis. But when jaundice has developed there should be a minimum of delay in establishing a diagnosis and initiating treatment.

When a man over 60 years of age develops pruritis and a steadily deepening jaundice with no bile in the stool, the odds are in favor of an obstructing lesion of the bile duct, probably carcinoma. Under these circumstances, unless there is a history of alcoholism, ingestion of a toxic substance, stigmata of cirrhosis, or a striking impairment of liver function tests in the first few weeks of jaundice, there should be no delay in advising exploration or at least peritoneoscopy. The latter procedure gives much information with a minimum of risk, expense, and disability and can be done as an "in and out" procedure without hospitalization. Although little can be determined as to the nature of the obstruction, the liver and gall bladder can be visualized, and obstructive jaundice usually can be differentiated from degenerative or metastatic disease of the liver. If necessary, biopsies of the liver can be taken through the peritoneoscope.

When the common bile duct and the pancreatic duct are completely obstructed the patient's ability to assimilate food is strikingly impaired, weight is lost rapidly, protein metabolism is disturbed, and the function of the liver soon deteriorates. Under these circumstances the risk of operation rises in direct proportion to the duration of the jaundice. After three months irreversible damage has been done, and preoperative preparation cannot be expected to lower the risk very much. Under such circumstances the operation must often be divided into stages, thereby increasing the technical difficulties and subjecting the patient to greater discomfort and expense.

The following case illustrates the advantage of early operation before irreversible damage has taken place.

Case Report

The patient, aged 78, was subjected to radical pancreatoduodenectomy two weeks after the onset of jaundice and left the hospital two weeks after operation. He had been well until four weeks before entry, when he developed upper abdominal pain, belching,

and nausea. His urine had been dark during this time, and a week before entry the stools had become white. Four days before entry he noticed jaundice and itching. He had lost 15 pounds in the past two years and 3 pounds in the past week.

Examination showed a well developed, well preserved, wiry man whose weight was 150 pounds and height 5 ft. 6¼ inches. The skin and sclerae were jaundiced, and the liver edge was palpable 2 fingers' breadth below the costal margin. A rounded mass suggestive of the gall bladder was palpable under the liver edges.

Roentgenograms of the chest and upper abdomen showed no abnormalities.

The icteric index was 120. Stools were acholic and contained excessive amounts of fat. There was bile but no urobilinogen in the urine, and the serum bilirubin was 27.8. The blood amylase and the prothrombin time were normal, as were the blood counts and serology.

Five days later the patient was admitted to the hospital. After three days of preparation which included a high-protein, low-fat diet and the administration of synthetic vitamin K, a radical pancreaticoduodenostomy was performed in one stage. All of the duodenum and the head and part of the body of the pancreas were removed. Continuity of the gastrointestinal, pancreatic, and biliary tracts was re-established in accordance with the technic shown in the figure.

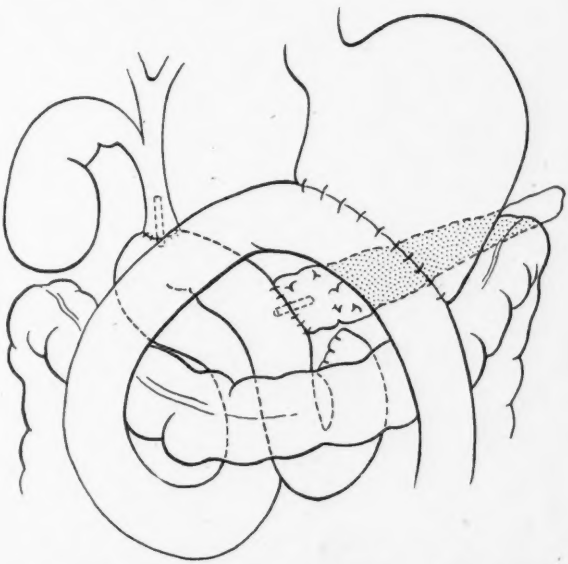

FIGURE. Radical resection of head of pancreas and duodenum, showing gastroenterostomy and implantation of pancreatic and biliary ducts into duodenum.

Convalescence was entirely uneventful, the maximum postoperative temperature never exceeding 100.5°. The patient left the hospital on the thirteenth day after operation with the jaundice subsiding. About ten days later he had an attack of severe epi-

gastric pain simulating biliary colic and a temperature of 101°. A roentgenogram showed that he had passed the catheter in the common duct over which the anastomosis had been made. The catheter was visualized in the colon. Convalescence from this time on was uneventful, and the patient rapidly regained strength. It is now four months since operation and he is free of symptoms and carrying on his work.

The pathologist reported the tumor an adenocarcinoma, fairly well differentiated, of the head of the pancreas. It is significant that two biopsies taken prior to resection showed nothing but fibrosis, further proof that a negative biopsy does not rule out deep seated carcinoma of the pancreas.

Summary

1. The lowered mortality rate following radical pancreatoduodenectomy for carcinoma of the head of the pancreas renders this the treatment of choice for carcinomas which have not metastasized or extended locally beyond the range of potential curability.

2. Even though the curability rate of carcinoma of the head of the pancreas is low, the striking palliation that follows resection and reimplantation of the pancreatic and bile ducts into the intestine and the optimism that arises from the knowledge that there is a chance of cure makes the operation of value in selected cases.

3. Carcinoma of the head of the pancreas is difficult to diagnose in its early stages either in the clinic or at the operating table.

4. The study of pancreatic ferments in the duodenum promises to aid in indicating an early obstructing carcinoma of the pancreatic duct, but this test is as yet somewhat unreliable.

5. When an elderly patient develops jaundice, his ability to survive operation diminishes rapidly, hence there should be no delay in establishing a diagnosis.

6. Radical pancreatoduodenectomy for a carcinoma of the pancreas occurring in a man 78 years of age is reported. The uneventful recovery is attributed to the fact that the operation was performed less than two weeks after the onset of jaundice.

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VASCULAR MALFORMATION OF THE SPINAL CORD

Report of a Case

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The occurrence of vascular malformations and vascular tumors of the spinal cord is perhaps sufficiently infrequent and interesting to justify the recording and discussion of a case which is unique in the experience of the writer. Most neurologists, through the writings of Lindau, Cushing, Bailey, Dandy, Olivecrona, and others, have become familiar with these conditions in the brain. However, except for single case reports or reports of small groups of cases, there has been no attempt until recent years to make a comprehensive study and classification of these vascular abnormalities of the spinal cord.

In 1941, O. A. Turner and J. W. Kernohan[1] reported a pathologic study of 46 cases of vascular malformations and tumors of the cord. In 1944 Wyburn-Mason[2] published a monograph entitled *The Vascular Abnormalities and Tumors of the Spinal Cord and Its Membranes* in which he presented a classification of these conditions, thoroughly discussed each type, and added 57 cases to the literature. A very complete bibliography has been included in his book. Prior to 1941 he had found only 140 cases in the literature. His classification is as follows:

(A) Abnormalities
- (I) Venous abnormalities
  - (a) Secondary venous abnormalities, that is, those occurring below a tumor of the cord or associated with arachnoiditis or calcification of the cord.
  - (b) Angioma racemosum venosum, that is, extensive venous varicosities affecting the pia and central regions of the cord.
- (II) Arterio-venous angioma
- (III) Arterial anomalies
  - (a) Associated with congenital heart disease.
  - (b) Alone.
- (IV) Syphilitic aneurysm of the spinal arteries.
- (V) Telangiectases, including so-called cavernomata or cavernous angiomata.

(B) True Tumors

(VI) Hemangioblastoma or hemangio-endothelioma.

(a) Angioreticuloma, or Lindau's tumor, occurs in the cord or on a nerve root and may be associated with syringomyelia, or with similar tumors elsewhere in the nervous system and cysts in other organs.

(b) Extradural hemangioblastoma.

(VII) Lymphangioma.

Arterial anomalies in the form of large tortuous collateral arteries, with or without the formation of a local aneurysm, may cause spinal cord compression in cases of coarctation of the aorta or patent ductus arteriosus. The case to be reported here, however, showed no evidence of congenital heart disease, and in view of the condition exposed at operation, it probably should be considered in the above classification as an arterial anomaly without congenital heart disease. Unlike 3 cases reported by Wyburn-Mason,[2] this case did not exhibit symptoms and signs of cord compression, but only those of nerve-root irritation, probably because of the low location of the lesion in the vicinity of the conus medullaris and cauda equina. The arterial anomaly appeared to be entirely extramedullary, and none of its constituent vessels was seen to penetrate the cord.

A word of caution regarding the surgical treatment of these vascular abnormalities of the cord may be worth-while. Radical attempts to excise, ligate, or coagulate these lesions should be avoided in most instances because of the danger of resultant degenerative changes in the cord due to alterations in blood supply.

Roentgen therapy is of little avail in the presence of vascular abnormalities which are composed of large vessels.

Case Report

A white man, aged 46, was first examined at the Clinic on May 11, 1946.

History. About eighteen months previously the patient had first experienced sharp pains in the calves of both legs. The pain was like a toothache and lasted three or four hours. A week later similar pain was experienced and lasted for two weeks. It was exaggerated by coughing and straining to move the bowels. Six weeks later pain recurred in the calves and also in the buttocks and lower back. The patient found it more comfortable to sleep while sitting up in a chair. Since that time he had had intermittent pain occurring in either buttock or leg. Two weeks before admission the patient had experienced severe pain in the left buttock, left popliteal area, left calf, and lower anterior surface of the left thigh. At the same time there was less severe pain of similar distribu-

tion on the right side. There had been no numbness, no loss of strength in the legs, and no loss of sphincter control.

During the eighteen months of pain experienced by this patient the following diagnoses had been made: sacro-iliac strain, neuritis, arthritis, male menopause, muscular sprain, and sciatica. The following forms of treatment had been carried out without relief: osteopathic and chiropractic adjustments, novocain injections in the sacro-iliac area, strapping of the back, and short-wave therapy.

General examination revealed a strong, healthy looking, middle-aged man, not acutely ill. There was no evidence of pulmonary, cardiac, or intra-abdominal disease. Rectal examination showed no masses, and there was no palpable evidence of prostatic neoplasm. Temperature was 98.1°, pulse 96, blood pressure 160/100. There was no evidence of zonal vascular abnormality or pigmentation of the skin.

Neurologic examination showed limited motion of the lumbar spine in all directions but no flattening of the normal lumbar curve and no list. The patellar and Achilles reflexes were very sluggish and equal on both sides. Motor function of the legs was normal. Sensation was normal throughout. There was no spasticity, no Babinski sign, and no clonus.

Roentgen examination of the lumbosacral region of the spine showed no increase in the width of the canal, no erosion of vertebral bodies or pedicles, and no other abnormalities.

Laboratory studies of the blood and urine, including the blood Wassermann reaction, were all normal.

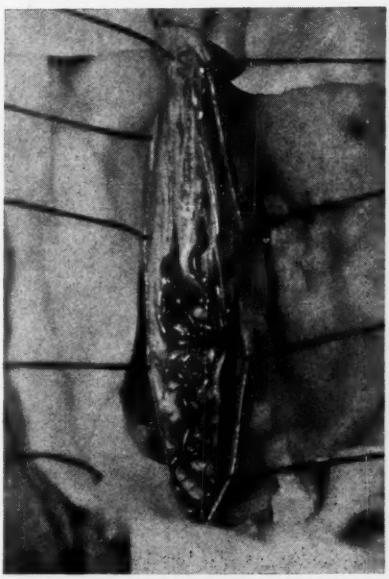

FIGURE. Vascular malformation of spinal cord.

Lumbar puncture between the second and third lumbar vertebrae on May 21, 1946, showed clear yellow cerebrospinal fluid at 170 mm. H_2O pressure. There was a complete spinal subarachnoid block by the Queckenstedt test. Only 1.5 cc. of fluid could be obtained for examination. This showed no cells, a trace of globulin, 4000 mg. total protein per 100 cc., and a negative Wassermann reaction.

Roentgen myelography was carried out after the introduction of 3 cc. of pantopaque into the lumbar subarachnoid space between the fourth and fifth lumbar vertebrae. The opaque medium failed to ascend in the spinal canal beyond the level of the third lumbar vertebra when the head of the patient was lowered on the fluoroscopic table.

As a result of the above clinical and laboratory data a diagnosis of intraspinal tumor was made. It seemed evident that its lower end did not extend below the level of the third lumbar vertebra. Laminectomy was advised and carried out on June 13, 1946. The spinous processes and laminae of the twelfth thoracic vertebra and of the upper three lumbar vertebrae were removed. The dura was opened in the midline throughout the length of the exposure, and through the transparent arachnoid large tortuous red blood vessels could be seen overlying the posterior aspect of the conus medullaris and extending downward among the strands of the cauda equina. When the arachnoid was opened, the serpentine mass of vessels was clearly visualized. The vessels were quite red in color and appeared to be slightly elevated above the surface of the cord. The largest vessels in the mass appeared to be about 1.5 mm. or 2.0 mm. in diameter. They did not appear to plunge into the substance of the cord, and several tortuous vessels extended downward below the lower limit of the exposure in close proximity to the strands of the cauda equina, especially on the left side of the spinal canal (figure). The tortuous mass of vessels overlying the conus medullaris appeared to extend upward beyond the upper limit of the exposure, but no attempt was made to enlarge the bony opening. It was impossible to determine from gross observation whether the vessels were arteries or veins, but it was the operator's impression that they were probably arteries. No aneurysmal dilatations were observed, and there was no evidence of any neoplasm such as a neurofibroma, meningioma, or ependymoma. It was considered inadvisable to attempt any radical removal of this vascular malformation. Ligation or electrocoagulation of the vessels in the mass might have resulted in serious neurologic dysfunction which was not present prior to operation. The dura was closed, and the soft parts were united in layers in the usual manner.

Following operation the patient received a course of roentgen therapy to the spinal cord and cauda in an effort to sclerose the vascular mass. He was discharged from the hospital on the seventeenth postoperative day without complications. He was last observed on August 31, 1946, at which time he stated that his pain was less severe than prior to operation and that he had returned to work on July 15. He did experience some pain on walking, but on the whole he felt definitely improved. His motor, sensory, and sphincteric functions were still normal, and his patellar and Achilles reflexes could not be elicited.

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SOME OBSERVATIONS CONCERNING PAIN IN THE NECK, UPPER CHEST, AND ARMS

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The diagnosis of the specific neurologic lesion that produces pain in the neck and arm may present a difficult problem. Obviously these pain impulses that arise centrally or peripherally mediate through the cervical or brachial plexuses. Since the type of cases we have under consideration involves the brachial plexus, and since the lesion is peripheral to the spinal cord, careful attention to this portion of the nervous system should be our first endeavor.

The brachial plexus is a somewhat intricate interlacement of the primary divisions of the lower four cervical nerves, the first thoracic nerve, and occasionally an added branch from the fourth cervical and second thoracic segments. These nerve radicles pass through the foramina of the spine and form fasciculi, which in turn pass downward between the scalenus anticus and medius muscles, then under the clavicle and into the apex of the axilla for distribution to the arm.

In peripheral lesions of this group of nerves we must differentiate first between the effects of pressure on the nerve radicles producing sensory changes such as pain and paresthesia of a segmental type and second, injury to the main nerve trunks. The principal causes of the former are lesions such as tumors, protruded disks, or osteophytes which involve or compress the nerve radicles in the spinal canal or within the spinal foramina. In the latter or peripheral brachial plexus lesions there are pathologic conditions producing pressure or irritation in the neck, axilla, or arm. Therefore, if one plots out the sensory changes in these areas of the skin, referring if necessary to neurologic charts, and if, in addition, examination is made for reflex changes, muscular atrophy, and vasomotor disturbances in the upper extremities, the site of the pathologic lesion can be determined with reasonable accuracy.

During our investigation it must be kept in mind that in segmental lesions there is an overlapping of the sensory fields so that a clear demarcation is not always possible. As a rule, two adjoining root segments must be involved to affect the entire sensory perception in any particular zone of sensation. Likewise, muscular atrophy or weakness may be indeterminate, since the motor innervation of a muscle is derived from more than one segment.

To repeat, segmental neuritis affects the roots within the spinal canal or within the foramina. Lesions in the first area may be due to pressure

of tumors or inflammatory processes such as herpes or arachnoiditis. In the second area (spinal foramina) the pressure is caused most commonly by herniated intervertebral disks or by osteo-arthritic changes. Proper interpretation is important since pressure within these foramina is amenable to surgical procedures.

For practical purposes the following symptoms and physical signs are indicative of radicular nerve pressure:

(1) Acute stabbing or shooting pain and paresthesia in the neck, shoulder, arm, and anterior or posterior area of the chest.

(2) Increase of pain by slight displacement of the cervical cord as the result of coughing, sneezing, or straining.

(3) Some relief of pain by a forward position of the head.

(4) Increase of pain by lateral bending of the head toward the side of the lesion, accompanied by pressure on the vertex of the skull.

(5) Temporary relief by bending the head to the opposite side.

(6) Increase of radicular pain by jugular vein compression.

(7) Sensory changes of a segmental distribution in the neck, chest, or arm.

(8) Reflex changes, muscular atrophy, fibrillation, all of which may result from pressure of long standing.

(9) X-ray findings of a narrowed intervertebral space usually associated with obliteration of the normal lordotic curve of the cervical region of the spine.

(10) Oblique films of the neck showing encroachment or narrowing of one or more foramina.

(11) Spinal fluid, cervical block, and increase in total protein above 40 mg. per cent.

(12) Myelogram showing a shadow defect at the site of the lesion.

Case Reports

Case 1. Herniated cervical disk. A man, aged 44, complained of attacks of pain in the left arm of one year's duration. There was no history of trauma. The discomfort was increased by coughing or straining and occurred in episodes thirty to forty times a day. It increased after the patient arose from bed and radiated over the left manubrium and anterior region of the chest but not into the left arm. However, he was conscious of paresthesia in the first three fingers of the left hand. There was no tenderness over either scalenus anticus muscle.

Bending of the head toward the side of pain did not increase the discomfort, but jugular compression produced sharp exacerbation of pain in the left arm and hand. Mild hypesthesia to touch and pin prick occurred in the upper posterior aspect of the

left shoulder, along the radial aspect of the left forearm and involving the first three fingers. These sensory changes varied from time to time. There was no muscular atrophy, fibrillation, or changes in the tendon reflexes of the arm.

X-ray films showed a straightening of the cervical region of the spine and a narrowing of the intervertebral space between the sixth and seventh cervical vertebrae. Oblique films showed encroachment of the foramen between the sixth and seventh cervical vertebrae by a bony spur.

Spinal puncture revealed clear, colorless fluid, normal dynamics, 4 cells, 41 mg. per cent total protein, and negative globulin, colloidal gold curve, Wassermann and Kahn tests.

Cervical laminectomy* revealed a protruded cervical disk between the sixth and seventh cervical vertebrae. This was removed.

Postoperatively the patient noted an increase in the paresthesia along the distribution of the seventh cervical segment. A few days following the application of a cervical plaster cast to support the head, the paresthesia disappeared. The cast was removed on the nineteenth postoperative day. Recovery was complete.

Comment

This case represents a milder form of cervical disk compression. Aside from the pain and paresthesia in the distribution of the seventh cervical nerve segment, the positive findings were an increase in symptoms accompanying jugular compression and x-ray signs of a narrowing of the intervertebral foramen. Prompt removal of the herniated disk spared the patient a long period of suffering.

Case 2. Cervical osteo-arthritis. A laborer, aged 59, developed pain in his right shoulder ten days before coming to the Clinic. The pain was constant and had developed gradually without any history of trauma. Motion of the head in all directions except forward caused exacerbation of pain, which manifested itself over the right interscapular area and into the right arm, chiefly in the radial area of the forearm and thumb. The pain decreased when the patient was lying down and was relieved somewhat when he supported his right elbow. Increase in painful symptoms followed pressure over the right brachial plexus and axilla. Jugular vein compression increased the pain. There was no Horner's syndrome, but increased sweating in the right hand was noted.

X-ray of the chest was normal; there was no evidence of cervical rib or superior sulcus tumor.

Cervical x-ray films revealed straightening of the cervical region of the spine. Oblique x-ray films showed cervical osteo-arthritis with narrowing of the joint space and foramina between the fifth and sixth cervical vertebrae.

Although the signs and symptoms suggested involvement of the foramina between the fifth cervical and thoracic vertebrae as well, a diagnosis of herniated disk between the fifth and sixth cervical vertebrae was made.

Laminectomy revealed a severe nerve root compression between the fifth and sixth cervical vertebrae by a herniated disk and an osteophyte. Surgical relief of pressure at

*Operation in referred cases by Dr. W. J. Gardner.

this point did not relieve the pain. Within three weeks considerable atrophy developed in the right triceps muscle (fifth and sixth cervical vertebrae).

At the second operation bony spurs were removed from the foramina between the fifth and sixth cervical vertebrae and the seventh cervical and thoracic vertebrae.

Crutchfield calipers were applied to the calvarium, and postoperative head traction relieved the pain and paresthesia. The patient was discharged wearing a leather cervical collar to support the head.

Comment

This case illustrates the contrast between herniated cervical disk, which rarely involves more than one intervertebral space, and osteoarthritis, which may produce pressure involving several metameres. Due to technical difficulties the simpler operation was performed at the foramen between the fifth and sixth cervical vertebrae but was not sufficient to give relief. It was necessary to reopen the incision and relieve nerve root pressure from the seventh and eighth metameres.

Lesions peripheral to the spinal column produce symptoms and physical signs quite different from those noted in the preceding case reports. Conditions such as injuries about the neck and shoulder, tumors above the clavicle or in the apex of the lung, cervical ribs, crutch paralysis, pressure on the brachial plexus by hypertrophied scalenus anticus muscles, aneurism of the subclavian artery, and even heart lesions must be considered in the differential diagnosis. Likewise, diseases of the lungs other than tumors and lesions in or below the diaphragm may cause pain in the neck.

Many cases in which there is obvious irritation of the brachial plexus require careful neurologic study. The following symptoms and signs comprise some of the important features of brachial nerve irritation.

(1) Radiation of pain and objective sensory disturbances along the cervical, radial, median, and ulnar nerves.

(2) Muscular atrophy or fibrillation of peripheral nerve distribution.

(3) Tendon reflex changes.

(4) Sympathetic nerve irritation or paralysis causing vasomotor trophic changes or Horner's syndrome.

Again by consulting various tables and charts in neurologic treatises the internist can readily determine which nerves are involved. The clinical findings in any particular case depend on the severity and duration of the pathologic changes in the nerves. It must be borne in mind that in experimental pressure on a nerve trunk the motor functions and various forms of sensitivity disappear in the following order: Proprioceptive impulses are blocked first; the impulses conveying pressure,

touch, pain, heat, cold, and vasoconstriction then disappear in this order. Reflex changes and muscular paralysis appear later.[1]

Case 3. Scalenus anticus syndrome. A male laborer, aged 29, began to notice pain associated with numbness and tingling in the third, fourth, and fifth fingers of the right hand three and one-half years before admission to the Clinic. The pain, while worse at night, was increased by use of the arm. When severe it spread to the shoulder and the right anterior upper area of the chest.

The physical findings consisted of hypalgesia of the right fourth and fifth fingers. Movement of the neck was not painful and did not affect the radial pulsations. Pressure over the right scalenus anticus elicited tenderness and increase of pain in the right hand. Pressure over both the right and left scalenus anticus muscles obliterated the radial pulses.

X-ray of the cervical region of the spine including oblique views showed no abnormality.

Right anterior scalenotomy was performed. The muscle was found to be thick and fibrous, especially over the brachial plexus.

Following operation the patient was relieved of all pain and noted only a transient numbness of the fingers.

Comment

There is considerable difference of opinion regarding the validity of a scalenus anticus syndrome. Anatomically the scalenus anticus muscle arises by four tendinous slips from the anterior tubercles of the transverse processes of the third to the sixth cervical vertebra. The four slips unite to form a flat muscle which extends downward and forward to be inserted into the scalene tubercle on the upper surface of the first rib. The nerve supply to the muscle is from branches of the fourth, fifth, and sixth cervical nerves. The scalenus anticus muscle lies in front of the roots of the brachial plexus, and near its insertion it passes over the second portion of the subclavian artery and under the subclavian vein. Therefore, in the event that there is increased backward pressure from spasm or hypertrophy of this muscle, especially in the presence of a cervical rib, we have the possibility of compression of the brachial plexus or subclavian artery.

Nachlas[2] doubts that this syndrome, which was first suggested by Adson and Coffey,[3] is a true pathologic entity. He believes that the scalene triangle formed by the cervical spine, the superior surface of the thorax, and the scalenus anticus muscle has two fixed sides and that this triangle is enlarged by spasm of the muscle. Thus any muscular pressure should relieve rather than exert pressure in the brachial plexus. Furthermore, he maintains that the benefit that may come from section of the scalenus anticus muscle is due to a better extension of the cervical area of the spine and an increase in the intervertebral foramina. In other

words, the symptoms attributed to this syndrome are due to radicular nerve pressure within the foramina.

On the other hand, our experience and many of the case reports in literature indicate that anterior scalenotomy gives relief not only of pain but also of vasomotor and anoxemic disturbances in the brachial nerve distribution. Regardless of anatomic considerations, anterior scalenotomy has practical value.

In our fourth and final case report we wish to discuss an uncommon but serious cause of pain in the neck and upper extremity. A tumor in the superior sulcus of the lung may produce pain of continuous and increasing degree without cough or respiratory symptoms. It is our experience that the cause of this pain is overlooked frequently, and the diagnosis is missed in the early stages of the disease unless one remembers to look for a Horner's syndrome and to take x-ray films of the lungs. A homogeneous shadow at the superior pulmonary sulcus on the side of the painful symptoms is usually diagnostic. An additional finding may be destruction of the first and second ribs. Since the tumor is malignant in type and usually resistant to x-ray therapy, the usual treatment is palliative, such as posterior rhizotomy or an attempt to cut the spinothalamic tracts on that side by cordotomy.

Case 4. Superior sulcus tumor (Pancoast). A man, aged 37, presented a long and disturbing history of pain in the right shoulder and arm. The symptoms began in August, 1944, after he had entered the Armed Services. It affected the right scapula and was increased by coughing, sneezing, and straining. The constant pain became more severe in November, 1944, and at that time a diagnosis of arthritis was entertained.

In the next six months the patient was studied at three Army hospitals and was discharged with the diagnosis of "hysteria" (patient's statement). Due to continued pain he was seen again at a veterans' hospital and granted 40 per cent disability.

The correct diagnosis was made by his home town physician, who remembered to take an x-ray of the lungs and discovered a right superior sulcus tumor. A course of radiation therapy given at this time failed to relieve the pain.

Operation performed in a Cleveland hospital consisted of biopsy and electrocoagulation of the tumor. The pathologic report was undifferentiated carcinoma.

Upon examination at the Clinic in February, 1946, the principal findings were: (1) pain and hyperesthesia in the distribution of the eighth cervical nerve and the first and second thoracic nerves, (2), increased pain by coughing and sneezing, (3) Horner's syndrome, right side, and (4) x-ray demonstration of a tumor of the right superior pulmonary sulcus. A rhizotomy, fifth cervical vertebra to the second thoracic vertebra, was performed on March 26, 1946, and on April 1, 1946, a cordotomy between the third and fourth cervical vertebrae was done. The pain was relieved somewhat but not completely.

Postoperative neurologic study showed that, while the right spino-thalamic tract was interrupted, the loss of pain, heat, and cold perception was not complete.

Comment

This case illustrates the long period of suffering (one and one-half years) that preceded discovery of the cause of pain. It is possible, of course, that a more careful neurologic study, especially with reference to Horner's syndrome, might have suggested the ultimate diagnosis. Cases of intractable pain present day and night should always suggest the possibility of a malignant tumor. While the surgical removal of a pulmonary superior sulcus tumor is seldom feasible, a cure by this means is possible if the diagnosis can be made in the very early stages of the disease.

Conclusions

We have presented clinical excerpts from 4 cases presenting a major symptom of pain in the neck, chest, and arm. Obviously there are many other pathologic lesions that produce cervical nerve root and brachial plexus irritation. However, careful anatomic and pathologic investigations will lead to the correct diagnosis in most instances.

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LONG SURVIVAL OF A PATIENT WITH CEREBELLAR MEDULLOBLASTOMA AND MALIGNANT GOITER TREATED BY ROENTGEN THERAPY

Report of a Case

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The following case report is of interest because the patient has survived eleven years following roentgen therapy for cerebellar medulloblastoma and four years following treatment for malignant adenoma of the thyroid gland.

Case Report

A woman, aged 27, was first seen at Cleveland Clinic Hospital by Dr. W. James Gardner on October 2, 1935. She was semicomatose, restless, and responded to questions only in monosyllables. She had divergent strabismus, papilledema, paresis of the left side of the face, left arm and leg, a positive Babinski sign, left patellar clonus, and bilateral ankle clonus. Laboratory examinations of blood and spinal fluid gave negative findings. The patient had no fever.

Five weeks prior to admission she had complained of attacks of frontal headaches which had increased in frequency and severity for at least a week, then changed in location to the occipital region. These attacks were associated with diplopia, vertigo, and occasional vomiting. She had given up her position as a public school music supervisor to rest in bed. Her symptoms had increased, however, and she entered a hospital and was examined by Dr. Louis J. Karnosh, who considered the diagnosis consistent with encephalomyelitis. He advised removal to Cleveland Clinic Hospital, where she was admitted in the condition described. Further questioning elicited the information that a few weeks prior to the onset of symptoms she had been struck on the head by a falling suitcase. This injury indicated the possibility of a frontal subdural hematoma.

On the third day after hospital admission the patient suddenly became somnolent and soon stopped breathing, although the pulse remained regular and of good quality. Artificial respiration and stimulants brought about normal respiration in about a half-hour, and she was taken to the operating room. A bilateral trephine was done over each parietal eminence. No evidence of hematoma could be found. Brain cannulas were inserted through the openings, and 90 cc. of cerebrospinal fluid was replaced by air. The wounds were closed and ventriculograms taken. The films revealed an obstructive hydrocephalus in the region of the fourth ventricle. A wide occipital craniotomy revealed a bulging mass in the left cerebellar hemisphere displacing the right lobe and herniating it through the foramen magnum. The aqueduct was patent. A brain cannula was introduced into the left cerebellar lobe, and at a depth of 4.0 cm. a cyst was drained of about 40 cc. of thick yellow fluid. As the patient's condition precluded other operative procedures, the wound was closed. A diagnosis of cystic glioma of the left cerebellar hemisphere was made.

Postoperatively she had headaches, and other signs of increased intracranial pressure necessitated one lumbar puncture and a few intravenous injections of sucrose solution.

Diplopia, nausea, and projectile vomiting persisted, and she had an attack of paroxysmal tachycardia. It was considered advisable to aspirate the cyst again under local anesthesia. At this time only a few drops of fluid were removed, and a fragment of necrotic tumor tissue was obtained for microscopic study. From this material Dr. Allen Graham made a diagnosis of medulloblastoma which has been confirmed by several other pathologists (fig. 1).

The patient was then given protracted roentgen therapy, the course being completed in December, 1935. Three areas of the occipital region were each given a total of 1350 roentgens (skin dose), the cervical, thoracic, and lumbar spinal areas each receiving 850 r. The physical factors were 200 Kv. and filter equivalent to 1.0 mm. h.v.l. copper. Four months later (April, 1936) the patient returned for a second course of roentgen therapy. She could walk without support, but change of position caused nausea. At the second course of treatment the occipital fields received 1500 r. and those along the spine each 600 r. She continued to improve and resumed teaching. Her gait was somewhat unsteady, and there were slight nystagmus and paresis of the left hand. A third course of roentgen therapy was given during January, 1937. The occipital fields received a total dose of 1200 r. and the spinal areas each 10,00[illegible] r. A summation of the amount of roentgen therapy administered in three courses during approximately two years (December, 1935, to January, 1937) shows that the external dose to the occipital region totaled 4050 r. through three fields. The tumor dose in the cerebellum approximated not less than 6000 r. In addition the spinal fields each received 2450 r.

During the next year the patient made good progress; however, nystagmus persisted, the Romberg test was positive, and she experienced difficulty in executing some movements on the piano with her left hand. She was seen periodically during the next few years, and gradually these conditions improved.

In August, 1941, a slight enlargement of the thyroid gland was noted. It was not considered significant until a year later when Dr. R. S. Dinsmore examined her and found enlargement of the left lobe of the thyroid gland and small nodules in the region of the posterior cervical lymph nodes. There had been no loss of weight or symptoms of hyperthyroidism. A biopsy was considered advisable, and a cervical gland was removed

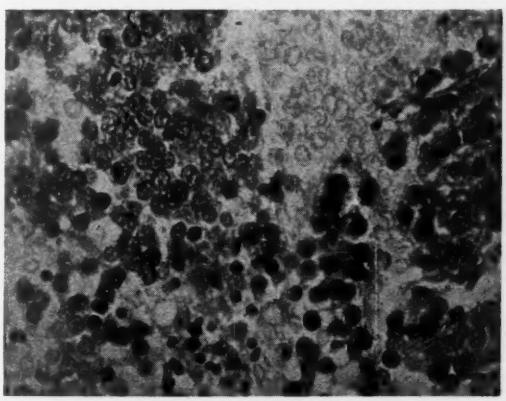
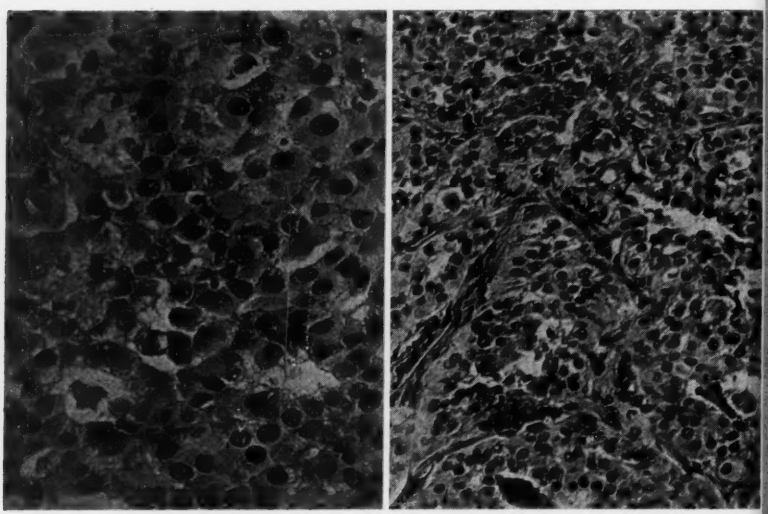


FIG. 1. Medulloblastoma. Showing uniform small cells, so-called medulloblasts, found in biopsy of cerebellar tumor x500.

for microscopic examination. Dr. Graham reported carcinoma of the thyroid gland, probably malignant adenoma (fig. 2). Thyroidectomy was considered inadvisable. The patient was given roentgen therapy to the left side of the neck, receiving 4000 r., with physical factors the same as before.

When she was seen recently (August, 1946) there was no evidence of recurrence of either the brain or thyroid gland tumors.



a *b*

Fig. 2. Carcinoma of thyroid, probably malignant adenoma type. Sections of tissue from biopsy of left cervical gland. Showing poorly developed lumen containing colloid (a) x250, (b) x500.

Although there are reports of patients with cerebellar medulloblastoma who have lived for as long as six years, the average survival rate is about two. In our experience we have seen very few young people with malignant disease of the thyroid gland who have survived more than two years.

CUTANEOUS BLASTOMYCOSIS

Report of Two Cases, One Being a Mucocutaneous Form

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Blastomycosis is an uncommon but well known chronic infectious disease produced by budding yeast-like organisms commonly grouped as blastomycetes. North American, South American, and European types have been described. Although the botanical classification of the various organisms producing the protean forms of the disease has not yet been clarified, a more recent and probably correct term for the causative organism of the North American type is Zymonema dermatitidis (blastomyces dermatitidis), for the South American types (paracoccidioidal granuloma) P. braziliensis, P. cerebriforme, and P. tenui (B. braziliensis), and for European blastomycosis, cryptococcus neoformans.[1] Since the latter two types do not originate in the United States this paper is concerned only with the North American type, under which the 2 cases herein described fall.

North American blastomycosis, as well as the other two types, occurs in two forms, systemic and cutaneous. Cutaneous lesions appear in 95 per cent of cases of the systemic form. A brief description of the clinical manifestations of the systemic form will bring into sharp relief those of primary cutaneous blastomycosis as exemplified by one of our 2 cases. The cutaneous lesions in systemic blastomycosis are probably hematogenous in origin, as they appear in successive crops of subcutaneous nodules and abscesses with subsequent development into ulcers having a purulent discharge. They tend to be disseminated on the unexposed parts such as the back, abdomen, and thighs, although the face and extremities may be involved.

In the cutaneous form the sites of predilection are the exposed surfaces, head, and neck, especially the face, hands, wrists, forearms, legs, and ankles, the frequency of sites in the order named. Owing to autoinoculation, multiple lesions are usually present. The eruption begins as a papulopustule that slowly increases in height and extent until it becomes a granulomatous lesion with a sharply elevated border. The surface is verrucous or papilliform with elevations and crypts which are covered with a crust. On removal of the crust miliary abscesses (crypts) which exude a somewhat mucilaginous, mucopurulent fluid of a dirty white color are exposed. The exposed surface bleeds readily. The border is

surrounded by a bluish-red, infiltrated zone in which miliary abscesses may be seen, although at times only with a magnifying glass. Occasionally the lesions are somewhat flat with a firm, dry, verrucous surface from which purulent material is obtained with some difficulty. The lesions are only slightly tender unless secondary infection results in more acute inflammation. Cutaneous blastomycosis does not spread to the regional lymph nodes nor to the blood stream, but occasionally systemic dissemination occurs.

There is a less superficial form of the cutaneous type called the gummatous type of cutaneous blastomycosis, in which the lesions originate in the deep corium or subcutaneous tissue. They are deep-seated, dark red, soft nodules surrounded by a violaceous zone of infiltrated skin. Other nodules appear in the periphery. Upon reaching the surface the lesions ulcerate, forming fungating masses. The ulcers are surrounded by the characteristic bluish-red borders containing miliary abscesses. Cutaneous blastomycosis is chronic and may continue over a period of years, although cures have been reported. Systemic blastomycosis, on the other hand, is highly fatal. Martin and Smith[2] state that 93 per cent of these patients die within three years after the onset of symptoms.

The exact habitat of Zymonema dermatitidis is unknown, but the organism is thought to be a plant saprophyte. Cases of blastomycosis have been reported from thirty states in the United States and from Canada. The majority occur in the section of the United States east of the Mississippi River and north of the southern boundaries of Tennessee and North Carolina. Outside of this section a goodly number have been reported from Louisiana. Persons have become infected in large cities as well as in the country. The disease occurs in slum districts and among people working in cellars and excavations, hide workers, milkers, stable employees, handlers of dead animals, railroad men, and farmers.

Martin and Smith[2] found in the literature one proved case of direct transmission of the disease in man. The inoculation occurred during a necropsy. Infections resulting from thorn pricks, chewing of blades of grass, and scratches from bramble bushes have been reported. Men are infected more often than women, the ratio being 9 to 1, and the age incidence of cutaneous blastomycosis ranges from 6 months to 80 years, the highest incidence in the third to the fifth decades and the peak in the fourth decade of life.

Histologically, primary cutaneous blastomycosis is characterized by irregular, papilliform, epithelial projections above the normal skin level. The surface is covered with dried pus, blood, and debris. There is extensive hyperplasia of the prickle cell layer, producing branching

down growths of various sizes and shapes. Numerous intra-epithelial abscesses are filled with polymorphonuclear leukocytes, red blood cells, an occasional giant cell, and often contain the causative yeast-like organisms. In the corium there are acute to chronic inflammatory changes with miliary abscesses. Occasionally a tubercle-like nodule with giant cells that often contain one or two of the organisms is present. The single and budding yeast-like cells are readily seen in hematoxylin and eosin sections or other stains, particularly methylene blue. Mycelial growth does not occur in tissue.

When pus from an abscess is placed on a microscopic slide and potassium hydroxide solution is added, the highly refractile, double-countered, single and budding organisms stand out. On culture mediums such as Sabouraud's and dextrose agar mycelial growth is obtained, while on blood agar incubated at 37° C. the yeast-like form is obtained. By subculture the yeast-like growth may be maintained on blood agar and kept in a refrigerator.

Of the 2 cases presented the first represents the typical primary cutaneous form of blastomycosis with multiple lesions; case 2, we believe, demonstrates the rarest form of cutaneous blastomycosis.

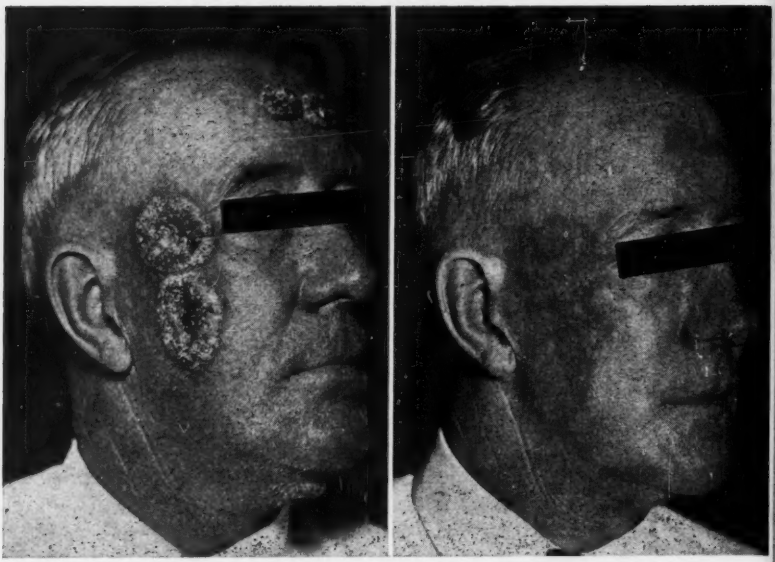
Case Reports

Case 1. (Fig. 1a) A white man and farmer, aged 60, came to the Clinic on November 3, 1941, presenting a number of growths on the face, trunk, and extremities. He lived in West Virginia and spent his working time between his grocery store and his farm. In June, 1941, he had first noticed two small, itchy red "mosquito bites" on the forehead. The lesions continued to grow in size, and during the next several weeks other "bites" appeared on the sides of the face, on the chin, elbow, left knee, and back. Growth of the lesions was regular and painless.

In September a positive blood serologic test for syphilis was discovered, and the patient was given antisyphilitic therapy including arsenicals, mercury rubs, and calomel. The lesions themselves were treated with roentgen rays. He had lost 26 pounds since June but felt in good health. He had had gonorrhea at the age of 20 but did not recall having had a chancre. The patient denied taking bromides or iodides.

The patient was obese but showed evidence of weight loss; otherwise, the general physical examination was normal. There were ten granulomatous growths on the cutaneous surface, two in the middle of the forehead, one just lateral to the right eyebrow, two on the left side of the face, two under the chin, one on the right forearm near the elbow, one on the upper part of the back, and one on the left patella. The lesions were annular and oval and from 2 to 5 cm. in diameter, rising abruptly to about 0.5 cm. from the skin surface. They were flat and covered with crusts beneath which were numerous tiny abscesses. The hairs were loose and easily lifted out of the lesions in the bearded region. From the bases of the lesions bluish-red zones extended peripherally for several millimeters and were studded with minute abscesses. The regional lymph nodes were not enlarged.

The hemogram and blood chemistry including bromine and iodine determinations were normal, and a chest roentgenogram showed normal findings. Droplets of pus were



a *b*

FIG. 1. Case 1 (a) November, 1941, (b) January, 1942. Showing the effect of iodide therapy.

mixed with a 20 per cent potassium hydroxide solution on a microscopic slide. A number of highly refractile, single, and budding organisms were readily seen under high power (fig. 2). Mycelian growths were obtained on cultures of the pus. The organism was considered to be Zymonema dermatitidis.

A small piece of one of the lesions was excised for histologic examination. The histopathology was typical of the description given in the preceding section.

Clinical course and treatment. As soon as the diagnosis was made the patient was given 1.3 Gm. (gr. 20) sodium iodide intravenously. Within twelve hours the lesions became swollen, red, and painful, but there were no toxic symptoms, and the reaction subsided in the next twelve hours. A saturated solution of potassium iodide was then administered in gradually increasing doses until the patient was taking 12 Gm. daily. In addition the lesions were treated with superficial unfiltered roentgen irradiations, 150 r. to each lesion. Antisyphilitic therapy was administered.

The patient was seen again in January, 1942, at which time the lesions had considerably healed (fig. 1b); however, the organisms were again obtained from miliary abscesses in several lesions. The patient was lost from observation after this visit.

Case 2. (Fig. 3.) A white man, aged 49, a resident of Ohio, came to the Clinic on April 1, 1946, complaining of hoarseness and a growth of three months' duration on the upper lip. The hoarseness was first noticed in December, 1945. In the beginning it was transient and slight but became progressively worse and continuous. About three weeks later a "cold sore" appeared on the upper lip, growing steadily in size and extent until it had invaded the nostrils, nose, and most of the upper lip. The involved nasal region became sore and painful. Concurrently, the hoarseness increased in severity. During the period from December, 1945, to April, 1946, the patient had lost about 4 pounds

and felt increasing weakness and loss of vitality. He was subject to frequent colds in the winter time. The patient was a boiler maker and worker in a railroad roundhouse. He could not recall having chewed straw or grass or twigs nor sustaining any injury about the mouth. A serologic test for syphilis in February, 1946, was negative.

The general physical examination revealed a well built and well nourished man. A large, dry, crusted granulomatous mass involved most of the upper lip, extended into the nostrils and to the tip of the nose. The surface was verruca-like and the color dull red. The margins of the lesion were sharp and perpendicular. There were a few small pustules at the mucocutaneous border of the left commissure. The vermilion border of the lip was invaded. The border was a dull bluish-red, and in it miliary abscesses were seen. In the mouth an extensive vegetating lesion involved most of the hard palate, and

FIG. 2. Photomicrograph, single and budding organisms under high power (x 450).

a number of small red papules were present on the buccal mucosa. There appeared to be no direct connection between this lesion and that on the lip and nose. On largyngoscopic examination a vegetating lesion appeared to involve the left half of the larynx, the true cord, and extended superiorly to include the false cord to the base of the epiglottis and the aryepiglottic fold. The left cord was in an abducted position and did not move on phonation. The lesion was covered with an exudate. The surface of the right vocal cord was somewhat rough.* The submaxillary lymph nodes were palpable bilaterally, which was thought to be due to secondary infection.

A roentgenogram of the chest showed normal findings, as did the hemogram, urinalysis, and blood chemistry, including bromine and iodine determinations. Blood Wassermann and Kahn tests were negative. A droplet of pus from an abscess in the lesion on the lip and on the hard palate was treated with 20 per cent potassium hydroxide solution, and numerous single budding yeast-like cells were found. Mycelial growth was obtained on culture. The organism was identified as Zymonema dermatitidis.

Clinical course and treatment. The patient was hospitalized for trial on penicillin therapy. After 1,700,000 units had been administered the lesions seemed to be less inflammatory but at the same time had increased in size and extent, while the regional lymph nodes had subsided to normal size. Sulfathiazole, 1 Gm. every four hours, and

*The laryngoscopic examination was made and lesions described by Dr. H. E. Harris of the Department of Otolaryngology.

urea, 30 Gm. every four hours, were administered for seven days. The blood level of sulfathiazole rose to 8.5 mg. and that of urea to 63 mg. per 100 cc. of blood, but the lesions showed no appreciable change. Upon discharge from the hospital the patient was given a saturated solution of potassium iodide. In June, 1946, the patient reported considerable improvement but has since been lost from observation.

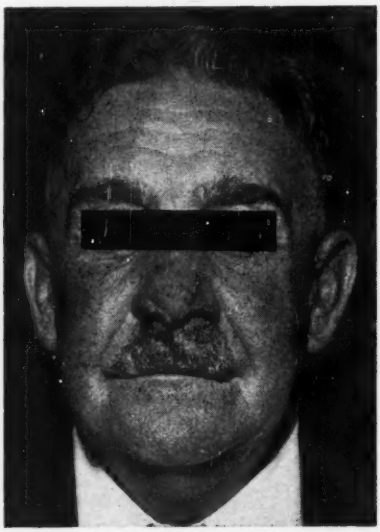


FIG. 3. Case 2. Cutaneous blastomycosis involving the upper lip and nose.

Comment

From the standpoint of diagnosis it was fortunate that the patient of case 1 had not been given iodides during the two months' treatment for syphilis before the diagnosis was established, otherwise the lesions would have been considered syphilitic by the response to treatment and may have been cured. According to Stokes,[3] cutaneous blastomycosis may at times be benefited by arsphenamine, and Ormsby and Montgomery[4] state that in some of their cases arsphenamine rendered the disease more responsive to iodides. This patient was treated with mapharsen (m-amino parahydroxyphenylarsine oxide), therefore it is a matter of speculation as to whether or not the drug has the same effect as arsphenamine. Notwithstanding the presence of a positive blood serologic test for syphilis and the history of gonorrhea some twenty years before, the papillomatous surface studded with miliary abscesses, the bluish-red border containing abscesses in contrast to the elegant arciform infiltrated borders of late syphilitic lesions, and the yeast-like cells

contained in the pus would have immediately disclosed the true nature of the disease.

Martin and Smith[2] caution against rapid treatment of blastomycosis before an estimate of the degree of hypersensitivity to the organism is made. They advocate preliminary hyposensitization with vaccines because mild to severe reactions may occur. In this case such a reaction occurred and was manifested by acute redness, swelling, pain, and tenderness of the lesions following the injection of sodium iodide.

We believe that case 2 presents a rare form of the disease. Martin and Smith,[2] in their review of 347 case reports, mentioned 1 case of laryngeal blastomycosis and a questionable case of blastomycosis of the larynx and vocal cords. Our belief that the primary site of inoculation was the larynx and vocal cords is based upon the chronology of symptoms in the history and the fact that there was no continuity of the lesions in the larynx, hard palate, and upper lip. It is possible that under a condition of ordinary extent of excursion of tidal air during the respiratory cycle one or several organisms would lodge on the "shelf" created by the vocal cords in the larynx. On the other hand, the patient could not recall having introduced any foreign objects into the mouth. Furthermore, because of the anatomic structure of the larynx and hard palate, lesions produced by more recent infection may give rise to symptoms here earlier than will older points of inoculation in the skin, where growth of lesions may proceed more slowly. Roentgenograms showed no evidence of lung involvement, and the patient showed no clinical symptoms of systemic infection. Hence it is unlikely that the lesions were secondary to a pulmonary infection.

In vitro experiments show that in order to obtain a partial inhibitory effect on the growth of Zymonema dermatitidis, concentrations of 50 mg. per 100 cc. or higher of the sulfonamides are necessary. This is about five times the concentration that may be safely maintained in the blood for any length of time. Franks and Taylor[5] reported the failure of sulfonamides and penicillin in systemic blastomycosis. Thus the failure of penicillin and sulfathiazole and urea is well demonstrated in this case.

Tuberculosis cutis (tuberculosis verrucosa cutis), cutaneous lesions of tertiary syphilis, bromide and iodide gummas, and carcinoma (epitheliomas) are most often confused with the cutaneous lesions of blastomycosis. Tuberculosis verrucosa cutis and cutaneous blastomycosis may at times be clinically indistinguishable, but the finding of m. tuberculosis on smear or culture and/or animal inoculation, increased skin sensitivity to tuberculin, and the histologic picture is in direct contrast with the finding of organisms of blastomycosis, and the histology only superficially resembles that of tuberculosis verrucosa cutis. Usually

the miliary abscesses in the border of the lesion of blastomycosis are not seen in tuberculosis verrucosa cutis. Syphilis complicating blastomycosis is a coincidence. The ulcerative gummas and late nodulo-ulcerative lesions of syphilis are not verrucous or papilliform and do not show miliary abscesses within or at the border. Bromide and iodide gummas are usually exquisitely tender and more painful than the lesions of blastomycosis, which produces only mild symptoms. The miliary abscesses are not found in the periphery of bromide or iodide gummas. A history of ingestion of bromides or iodides is almost always obtained, and iodides and bromides are frequently present in high concentrations in the blood. Epitheliomas present a smooth border in which telangiectasis is seen. The border is nodular and pearly and does not contain miliary abscesses. The surface of a skin carcinoma when ulcerated is granular rather than papilliform and does not contain miliary abscesses. There are no miliary abscesses at the periphery, as in blastomycosis. The histologic picture of carcinoma is characteristic. The finding of the yeast-like organisms in the pus and tissue sections of a lesion suspected of being blastomycosis establishes the diagnosis.

Summary

Two cases of North American blastomycosis are described. One case was of the primary cutaneous form, the initial lesions located on the forehead and the others produced by auto-inoculation. The coincidental discovery of a positive blood serologic test for syphilis led to antisyphilitic therapy. However, the fact that iodide was not administered made it possible to establish the diagnosis, which otherwise might have been confused and delayed for a considerable period. A mild Herxheimer reaction resulted from initial rapid treatment but could have been avoided by slow treatment with gradually increasing doses of potassium iodide. The second case we believe to have demonstrated a rare form of the disease, the initial lesions originating in the larynx and the mouth, and lip lesions occurring later. This case represents the mucocutaneous form of cutaneous blastomycosis. Zymonema dermatitidis was found in the pus on culture and in tissue sections in both cases.

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ALLERGY OF THE SALIVARY GLANDS

Report of a Case

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Section on Allergy

It is generally accepted that the clinical manifestations of hypersensitivity are numerous and diversified. To the typical allergic states of hay fever, bronchial asthma, perennial allergic rhinitis, and atopic eczema has been added a long list of phenomena less well understood, including certain cases of urticaria, some cases of migraine, many ocular problems, purpura, and a number of others. In such lists, however, allergy of the salivary glands receives scant attention. It is for that reason that the following case report is of interest and challenges admission to the family of allergic diseases.

Case Report

A white woman, aged 45, reported to the Department of Otolaryngology of Cleveland Clinic on March 12, 1946, with two complaints. For ten years nasal breathing had been difficult and was associated with frequent sneezing and profuse rhinorrhea. In addition, for the preceding four years she had experienced swelling followed by cramping pain around the angles of the jaw, relieved later by a discharge of foamy whitish material into her mouth. This frequently caused eating to be painful.

Nose and throat examination revealed large, pale, boggy turbinates bathed with mucus. No other significant findings were noted. The duct of either the submaxillary or the parotid glands had been dilated and probed previously with negative results.

A roentgenogram of the left parotid and submaxillary regions was taken revealing no evidence of calcification. In view of the history of allergy, the patient was advised to proceed with allergy studies.

Extensive questioning revealed additional evidence of hypersensitivity. The above nasal symptoms had continued more or less daily at all seasons but increased during the winter months. She had discovered that contact with dust, feathers, wool, and cigarette smoke produced these symptoms, as did several foods, including wheat.

About two years later the patient had developed generalized urticaria accompanied by angioneurotic edema of the eyelids and lips. Symptoms had persisted daily for ten months, then ceased. At intervals of several months since, however, she had had a few urticarial lesions, usually traceable to ingestion of chocolate, and on one occasion, cantaloupe.

In the past four years she had suffered recurring painful swellings about the angles of the jaw, both unilaterally and bilaterally. These recurred every week or two, lasting for two or three days. She could obtain some relief by massaging the swollen area, noting a discharge of "salty saliva" into her mouth. She had observed that eating of wheat, cheese, tomato, and chocolate produced such swellings and, in addition, nausea. These same foods aggravated her nasal symptoms.

The family history was positive for allergy. Her father had hay fever and asthma.

Physical examination disclosed some tenderness over each parotid gland but was otherwise negative except for the pale, swollen nasal mucous membranes typical of allergy. Routine urinalysis and blood counts were within normal limits.

Complete allergy investigation was carried out, using both scratch and intradermal methods of testing. Pollen reactions were quite negative. Intradermal tests for inhalants revealed strongly positive reactions to house dust and cotton, with positive reactions also to feathers, cat, dog, and horse dander, Pyrethrum, silk, tobacco, and Aspergillus mold. A questionable reaction was obtained to wool. Intradermal food tests were positive to chocolate, oat, buckwheat, barley, cherry, peas, several varieties of nuts, cabbage, cauliflower, mushroom, onion, hops, and several kinds of fish. Questionable reactions were obtained to wheat, cheese, tomato, and potato.

The patient was carefully instructed in the details of an allergy regime, avoiding all significant inhalant allergens as far as possible and the foods to which she reacted. Adequate, regular rest was advised. Hyposensitization was begun with a mixed antigen of dust, cotton, and molds, in a dilution of 1:10,000; a stock vaccine of stool, respiratory, and various pathogenic organisms in 1:1000 dilution was also given. She reported improved five weeks later, and the next strong dilution of each of the above was furnished with instructions to continue.

Two and a half months after institution of the allergy regime the patient reported excellent results and stated that so long as she adhered strictly to her diet she had no trouble with her glands. However, if she ate the foods that were not permitted, there was a recurrence of the swelling. She felt that dietary avoidance had been more important than the injections.

Discussion

Although the literature on allergy is already quite voluminous, a fairly careful survey reveals few references to allergy involving the salivary glands. In his comprehensive book Vaughan[1] fails to mention it, as do authors of several other large texts on allergy. Feinberg[2] indicates that "swelling and inflammation of the salivary glands, particularly the parotids, occurs occasionally in some individuals as a result of the administration of iodides". He registers some doubt as to whether or not this should be regarded as an allergic phenomenon, but states that the condition appears only in a small group and reappears every time iodine is administered. In a recent publication by the Staff of Cleveland Clinic[3] in which many uncommon manifestations of allergy are discussed, this problem is not mentioned.

Likewise, the ear, nose, and throat literature deals very cursorily with the subject, many authors failing to mention it. Jackson and Jackson[4] mention recurring swelling of the parotid and submaxillary glands, recognized as being associated at times with hay fever and perennial allergy of the nose and paranasal sinuses.

The case reported seems unquestionably due to an allergy involving the salivary glands, probably the parotids. An obstruction, such as a

stone in the duct or a growth, was excluded first by the otolaryngological department. The patient had a typical history and findings to substantiate a nasal allergy for many years. Urticaria had also recurred periodically for several years and could frequently be traced to ingestion of certain foods. The periodic swelling of the glands would likewise follow the eating of several foods and could be avoided later by careful adherence to an allergy diet and regime. They would recur when the diet was broken. In this case the family history of allergy formed another link in the presumptive diagnosis of allergy.

Conclusion

A case is reported of recurrent swelling of the salivary glands, probably the parotid glands, with the strongest presumptive evidence that allergy is the etiologic factor. Symptoms could be controlled by an allergy regime, especially avoidance of incriminated foods, and reproduced by ingestion of such foods.

It seems worth-while to reiterate that when a patient presents a problem difficult of diagnosis and has a positive personal history of allergy and/or a positive family history of allergy, consideration of allergy as the etiologic factor is strongly indicated.

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THE DIAGNOSIS OF ESOPHAGEAL VARICES IN PORTAL HYPERTENSION

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The roentgen demonstration of esophageal varices is important in establishing a diagnosis of portal hypertension. In atypical cases varices may be the first demonstrable evidence of this disease. The roentgen demonstration of varices may be difficult and will frequently be missed if a thorough examination of the esophagus is not made. Recent advances in the clinical management of portal hypertension and in the control of hemorrhage from esophageal varices by surgical procedures render an early diagnosis essential in the treatment of this condition.

We have reviewed a series of 25 cases with an established diagnosis of portal hypertension. These cases re-emphasize the clinical and diagnostic features that have been described by Schatzki, [1,2] Templeton,[3] and other writers. [4,5,6] Two case reports which stress the importance of the roentgen demonstration of varices are presented.

The physiologic changes that take place in the development of esophageal varices have been demonstrated by McIndoe[7] and Kegaries.[8] In the presence of obstruction to the portal system a collateral circulation returns the venous blood to the systemic circulation. The most common route of this venous return is through the communications between the coronary vein of the stomach, the splenic vein, and the esophageal venous plexus. Obstruction to the portal system, such as occurs in cirrhosis or in thrombosis of the splenic vein, results in an increase in pressure and in a reverse of the flow of blood through the coronary vein and the esophageal venous plexus. As a result of this, varices develop. The coronary veins are less susceptible to dilatation because of the supportive connective tissue and consequently are infrequently demonstrated. On the other hand, the loose connective tissue of the esophagus permits the veins to dilate. Esophageal varices frequently bleed because the veins may lie immediately beneath the mucosa and are subjected to the trauma associated with esophageal function.

Roentgen Diagnosis of Esophageal Varices

The roentgen demonstration of varices requires considerable care and time. Attention should be directed to the lower third of the esophagus immediately above the cardia. Varices can occur throughout the

esophagus but appear first in this region. We have not observed varices in that portion of the esophagus below the cardia.

X-ray examination must be carried out in both the erect and recumbent position. We have found that the horizontal position is essential and that both regular and medium-thick barium should be used. The barium-filled esophagus will obscure early and moderate-sized varices. The diagnosis is dependent on obtaining a thin coating of barium on the mucosal folds of the relaxed esophagus, in which condition the tortuous and irregular polypoid-like changes are best demonstrated. Occasionally barium regurgitating from the stomach, with or without the Valsalva test, provides this thin coating. The barium-filled esophagus permits diagnosis of only large varices, which produce an inconstant, serrated appearance of the walls.

It is not uncommon to note slight dilation of the lower esophagus and some hesitancy in the emptying of barium through the cardia. On the other hand, active peristalsis may completely empty the esophagus as well as contract the dilated veins. Under such conditions the varices may be obscured.

Fluoroscopic observation cannot be relied upon for the diagnosis of varices. It is necessary to supplement fluoroscopy with serial spot films or multiple survey films. Films should be made in both the AP and oblique positions following a swallow of medium-thick barium. Because of the technical difficulties a second roentgen examination or esophagoscopy may be necessary to establish a diagnosis.

Esophageal varices can usually be differentiated from other lesions of the esophagus by the inconstant character of the defects, the obliteration of the defects by peristalsis, and the presence of flexible walls.

Some indication of the incidence of varices is given by Schatzki.[1] He found that esophageal varices are demonstrable by x-ray in 50 per cent of all cases of cirrhosis and that the percentage is higher in advanced cases with splenomegaly, ascites, or hematemesis.

Clinical Importance of Demonstration of Varices

Case Reports

Two case histories from our series of 25 are briefly reviewed to illustrate the importance of roentgen demonstration of esophageal varices.

Case 1. A man, aged 41, entered Cleveland Clinic Hospital in August, 1945. He gave a history of tarry stools occurring intermittently over a period of one and a half years. He had experienced the first attack in 1944 and because of associated weakness and loss of blood had required several transfusions. X-ray examination of the esophagus,

stomach, and duodenum following the first attack was reported negative except for a "spastic duodenal cap". In June, 1945, he had had recurrent attacks of bleeding. transfusions were required, and an exploratory operation was performed. The stomach and duodenum were normal, but changes in the liver suggested early cirrhosis. A biopsy of the liver was reported as showing evidence of parenchymatous degeneration, but evidence was not conclusive for cirrhosis. Following operation he had experienced recurring tarry stools.

At the time of admission, the clinical examination was negative except for evidence of anemia and very questionable evidence of enlarged spleen. The liver was not palpable. There was no history of abdominal pain or vomiting. The laboratory tests showed a hypochromic anemia (red blood cell count 3,810,000; hemoglobin 9.9 Gm.), increased bromsulphalein retention (36 per cent in thirty minutes), and decreased total serum protein (6.4 Gm.). X-ray examination demonstrated moderately large varices in the esophagus, confirming the evidence of portal hypertension (fig. 1, 2). During the next year the patient had repeated esophagoscopies with injection of the varices, the last injection being done on November 25, 1945, at which time he appeared in moderately good condition.

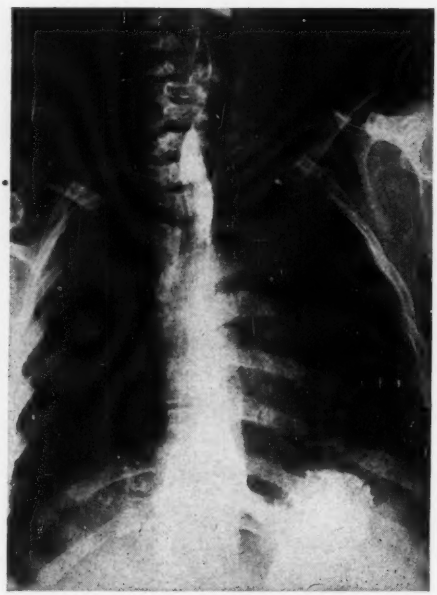
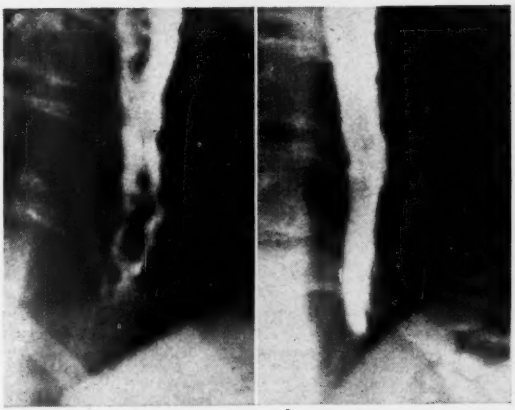


Fig. 1. Varices are obscured by retained barium in the esophagus.

This case illustrates that the diagnosis of portal hypertension must be considered despite the absence of an enlarged liver or the absence of ascites. It emphasizes the importance of checking the x-ray findings in cases of unexplained bleeding. Adequate x-ray examination might



a *b*

FIG. 2. (a) Polypoid appearance of esophageal varices with a thin coating of barium. (b) Same, showing obliteration of varices by barium.

have established the diagnosis of varices at the original examination and avoided an exploratory operation.

Case 2. A man, aged 40, was admitted to Cleveland Clinic Hospital on August 14, 1944, complaining of recurrent attacks of nausea, vomiting, and weakness during a two-year period. Intermittent fever (102° and 103°) and vague abdominal pain had begun to occur at the end of this time. The patient had lost 60 pounds in weight, and repeated blood examinations had shown a progressive anemia. Therapy had consisted of three courses of sulfa drugs and five injections of penicillin as well as supportive therapy.

Upon admission, physical examination was negative except for evidence of anemia, fever (101°), and an enlarged spleen. Laboratory studies showed a hypochromic anemia (3,060,000; 6.8 Gm. hemoglobin), a leukocytosis of 16,550 (90 per cent neutrophils, 6 per cent lymphocytes; 4 per cent monocytes). The icteric index was 4, and a bone marrow puncture was not diagnostic. Stool examination for occult blood was positive, and x-ray examination of the gastrointestinal tract demonstrated esophageal varices. A nonfunctioning gall bladder was also found. Following blood transfusions the patient was discharged.

He returned to the Clinic two months later (October 18, 1944), stating that he had had recurrent attacks of fever (104°) and, for the first time, hematemesis. The bromsulphalein test showed a retention of 32 per cent in thirty minutes. The spleen was large, the liver not palpable. A final diagnosis of portal hypertension, possibly due to thrombosis of the splenic vessels, was made. Splenectomy was advised and performed elsewhere. Subsequently the patient had the varices injected by esophagoscopy on three different occasions between August 16 and November 29, 1945. At the last injection it was noted that the varices were much less prominent. In a follow-up letter on December 7, 1946, the patient reported that his general condition had remained good and that there had been no subsequent bleeding.

The clinical picture of this patient complicated the diagnosis. Roentgenologic demonstration of varices was the prominent feature in establishing a diagnosis, emphasizing the importance of an adequate x-ray examination of the esophagus in all patients.

Summary

1. It has been shown that portal hypertension may be first suspected by the roentgen demonstration of esophageal varices.

2. The roentgen technic necessary to demonstrate varices is emphasized.

3. Two case histories from this series of 25 have been reported.

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THE FRANK E. BUNTS INSTITUTE

Tentative Program

Blood, Bleeding, and the Blood Vessels

Sunday, March 16, 1947

9:00...Dr. R. H. McDonald....Medical Management of Intracranial Hemorrhage
9:30...Dr. W. A. Nosik.....Surgical Management of Intracranial Hemorrhage
10:00...Dr. H. E. Harris.....Hemoptysis
10:30...Dr. H. R. Rossmiller....Hematemesis
11:00...Dr. P. M. Moore, Jr.....Hemorrhage from Nose
11:30...Dr. T. E. Jones.....Hemorrhage from Bowel
12:30...Lunch
2:00...Dr. W. J. Engel.....Hemorrhage from Genitourinary Tract
2:30...Dr. J. C. Root.....Bleeding Lesions of Small Bowel (Roentgenologic Study)
3:00...Dr. A. D. Ruedemann....Ocular Hemorrhage
3:30...Dr. E. P. McCullagh....Metrorrhagia and Menorrhagia
4:00...Dr. I. H. Page.....Hemorrhage and Shock
4:30...Dr. R. S. Dinsmore.....Surgical Aspects of Splenectomy

Monday, March 17, 1947

9:00...Dr. R. D. Taylor.....Medical Treatment of Hypertension
9:30...Dr. W. J. Gardner.....Surgical Treatment of Hypertension
10:00...Dr. A. C. Corcoran.....The Kidney in Hypertension
10:30...Dr. Fay LeFevre.....Peripheral Vascular Disease
11:00...Dr. John Tucker.....Vascular Headache
11:30...Dr. R. W. Schneider.....Vascular Disease in Diabetes
12:30...Lunch
2:00...Dr. A. C. Ernstene.....Diagnosis and Treatment of Coronary Disease
2:30...Dr. J. B. Hazard.....Pathology in Arterial Disease
3:00...Dr. R. J. Kennedy.....Eye Changes in Vascular Disease
3:30...Dr. G. H. Williams, Jr...Cerebral Arteriosclerosis
4:00...Dr. C. R. K. Johnston....Allergic Changes in Blood Vessels
4:30...Dr. W. J. Zeiter.....Physical Therapy in Vascular Disease
6:30...Dinner Meeting

Dr. C. C. Sturgis.....Pernicious Anemia
Professor of Internal Medicine
University of Michigan,
Ann Arbor, Michigan

Tuesday, March 18, 1947

9:00...Dr. E. W. Netherton....Acute Disseminated Lupus Erythematosus
9:30...Dr. E. N. Collins.....Anemia in Gastrointestinal Diseases
10:00...Dr. R. L. Haden.....Anemias of Obscure Origin
10:30...Dr. L. W. Diggs.....Sternal Puncture
11:00...Dr. George Crile, Jr....Thrombophlebitis and Embolism
11:30...Dr. D. E. Hale.....Bleeding to Control Hemorrhage
12:30...Lunch
2:00...Dr. A. T. Bunts.....Vascular Tumors of Nervous System
2:30...Dr. U. V. Portmann.....Treatment of Vascular Nevi
3:00...Dr. L. J. Karnosh.....Vasomotor Disturbances of Face
3:30...Dr. C. C. Higgins.....Aberrant Renal Vessels
4:00...Dr. J. I. Kendrick.....Surgical Treatment of Gangrene
8:00...David Dietz.....The Lesson of Bikini
Scripps-Howard Science Editor

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....., 1947

The Frank E. Bunts Institute
Cleveland Clinic
East 93rd Street and Euclid Avenue
Cleveland 6, Ohio

Gentlemen:

Please register me for the course on "Blood, Bleeding, and the Blood Vessels" which is to be given March 16, 17, 18, 1947.

I am sending check for $5.00, and the remainder of the fee, $5.00, will be paid on Registration, March 16.

NOTE: Checks should be made payable to the Frank E. Bunts Institute and sent to A. D. Ruedemann, M.D., Cleveland Clinic, Cleveland, Ohio.

Name.....

Address.....

Medical School and
date of graduation.....

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